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Synthesis of glycosylated aminothiol from D-glucose as promising anti-tubercular agent

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A facile method for a series of novel glycosylated β-aminothiols by employing TBAB/NEt_3-catalyzed ring opening of thiirane ring of D-glucose-derived 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose with different primary and secondary amines including aliphatic, aromatic, heterocyclic, and glycosyl amine has been devised. Diamines on the other hand for thiirane ring opening of anhydroglucose derivative led to the formation of respective bis-glycosylated N^1,N^n-diaminothiols in good yield. The method is straight forward, economical, high-yielding and easy to scale up. One of the glycosylated aminothiol contains both the hydrophilic carbohydrate moiety and hydrophobic hexadecyl residue, thus can serve a promising candidate to exhibit surface-active properties. The resulted glycosylated β-aminothiols may serve as an interesting scaffold to develop mechanism-based novel chemotherapeutic agents.

Keywords: Glycosyl thiirane, oxirane, glycosyl aminothiol, diaminothiols, tuberculosis, surfactant.

Introduction

Owing to their important biological roles, including cell-cell interactions, cell growth, inflammation, and other physiological processes, carbohydrate-based molecules are well recognized scaffolds in medicinal chemistry[1–8]. The structural diversity arises due to versatility in functional groups and linkages has made them to play clinically vital role in drug discovery and development[8]. Furthermore their inherent hydrophilic/hydrophobic nature plays imperative function for good ADME parameters with minimal toxicity. Therefore, these characteristics have extensively been explored and tuned to generate a library of compounds for instant biological screening to develop the most effective and also economically viable lead drug molecules[2–4].

Aminothiols comprise another noteworthy class of compounds due to their diverse pharmacological and synthetic attributes. Some of them, especially cysteine, homocysteine, cysteamine, and penicillamine are the most widespread naturally occurring structures, featured in many complex biomolecules and drugs such as peptides, coenzyme A, antihypertensive agents[9], cytoprotectant amifostines[10–12], and have anti-tumor activities revealing RAS protein farnesyl transferase inhibitors[13,14]. Some naturally occurring β-aminothiol containing bioactive molecules have been depicted in Fig. 1. The installation of aminothiols on carbohydrate will improve the biological and physicochemical specificities due to the acidic nature and metal affinity of thiol group with good ADME functions[15]. Therefore, carbohydrate-based amino-

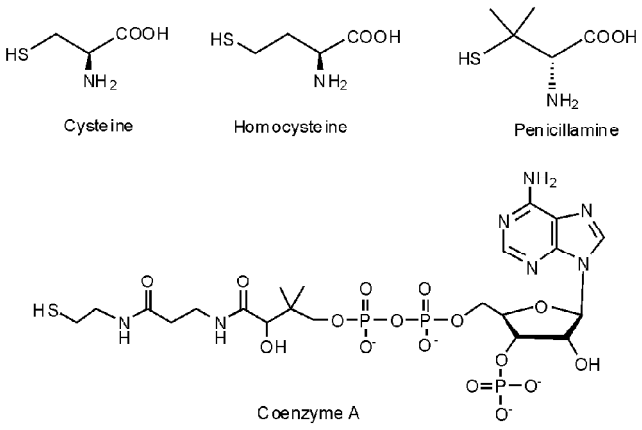
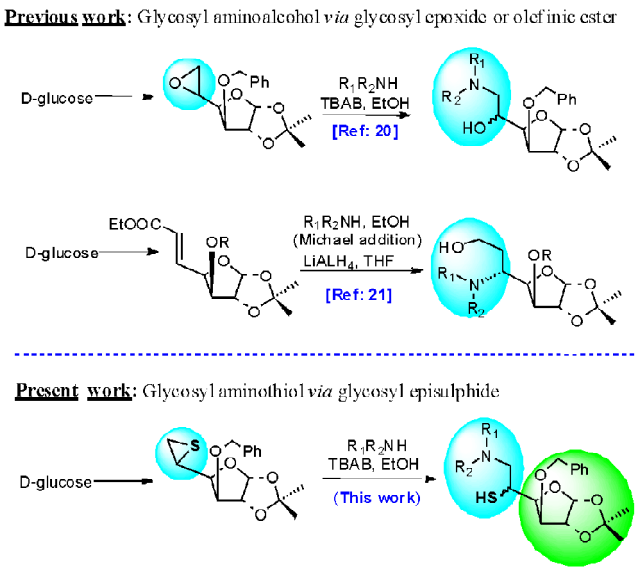


Fig. 1. Structure of few representative naturally occurring aminothiols.

thiols are of paramount importance for the development of lead drug molecules.

Most of the methods reported are for non-carbohydrate based aminothiols and require cumbersome steps like protection/deportation of amino and thiol groups[16], whereas other developed methods suffer with the limitation of less accessible precursors such as thiazoline[17], aziridines[18], and 2-thiazolidinones[19]. To the best of our knowledge, no report so far has described the synthesis of carbohydrate-based β-aminothiols. In our previous work, we had successfully prepared glycosyl β-aminoalcohols from D-glucose via glycosyl oxirane which prompted us to extend the methodology to β-aminothiols (Scheme 1)[20]. Other related glycosylated β-aminoalcohols were also obtained via conjugate addition of amines to glycosyl olefinic acid followed by LAH reduction of resulted glycosylated β-amino ester[21].

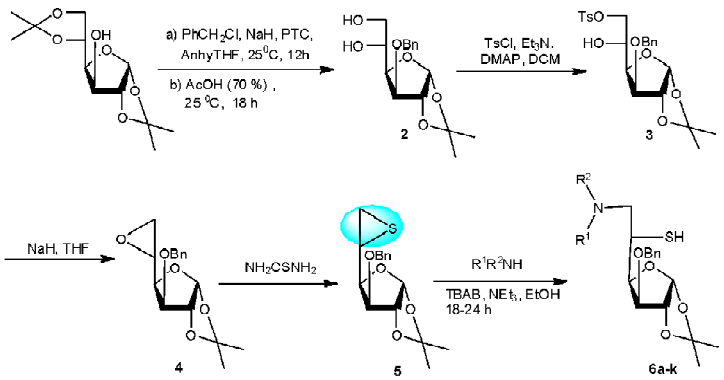
Herein, we wish to report an efficient and general method for the synthesis of glycosyl β-aminothiols from D-glucose via glycosyl thiirane. The method utilizes simple starting materials which are easily accessible and reaction is easy to handle that establish the scope of the reaction as the practical one. The resulted carbohydrate-based molecules are biologically relevant and can be explored in order to get new chemical entities for further development.



Scheme 1. Our previous route to synthesize glycosyl β-aminoalcohols from D-glucose via glycosyloxirane and glycosylated olefinic ester.

Results and discussion

The strategy began with the synthesis of glycosyl aminoalcohol from 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**2**), derived from D-glucose in three steps including, acetonide protection followed by 3-*O*-benzyl protection using benzyl chloride and finally the selective tosylation with *p*-tosyl chloride in the presence of *N*, *N*-dimethylaminopyridine (DMAP) and Et_3N in anhydrous dichloromethane to afford mono-tosylated product **3** in high yield. The trace amount of ditosylated product was also obtained. The tosylated compound **3** was then treated with a number of nucleophiles/bases including sodium azide, DBU, NEt_3 and potassium tert-butoxide to afford 5,6-glycosyl oxirane **4** via cycloelimination under the catalysis of NaH in anhydrous THF condition. Reaction of oxirane with thiourea in methanol resulted in the formation of glycosyl thiirane **5** in good yield as the desired scaffold (Scheme 2). The reaction



Scheme 2. Synthesis of glycosyl aminothiols (**6a-k**) from D-glucose via glycosyl thiirane **5**.

of epoxide **4** with thiourea in a polar solvent like MeOH is presumed to occur with inversion of configuration at C-5 in accordance with the literature[22]. The structure of compound **5** was established on the basis of its spectroscopic data, including ^{1}H NMR, ^{13}C NMR and MS. Disappearance of methyl peak (Ar-Me) and four Ar-*H* in the ^{1}H NMR spectrum of compound **5** confirmed that tosyl group was eliminated from the parent molecule **4**. ^{1}H NMR spectrum of glycosyl thiirane **5** shows a multiplet at δ 3.24–3.18 for C-5 and two doublets for two protons of C-6 couple with each other at δ 2.38 and 2.09, whereas all other peaks in the ^{1}H NMR and ^{13}C NMR of compound **5** were observed in the expected range (Fig. 2).

After having established the optimized reaction conditions for an easy access of glycosyl thiirane, we proceeded for nucleophilic opening of thiirane ring with different aliphatic and aromatic amines. Opening of thiirane ring with various amines was carried out under different reaction conditions. The nature of the catalysts [DBU, *t*-BtOK, TBAB], the solvents (anhydrous DMF, anhydrous CH_2Cl_2, EtOH, H_2O), temperature (room temperature to 100°C), and reaction time were screened. Finally, a better result for aminolysis with 3-*O*-ben-

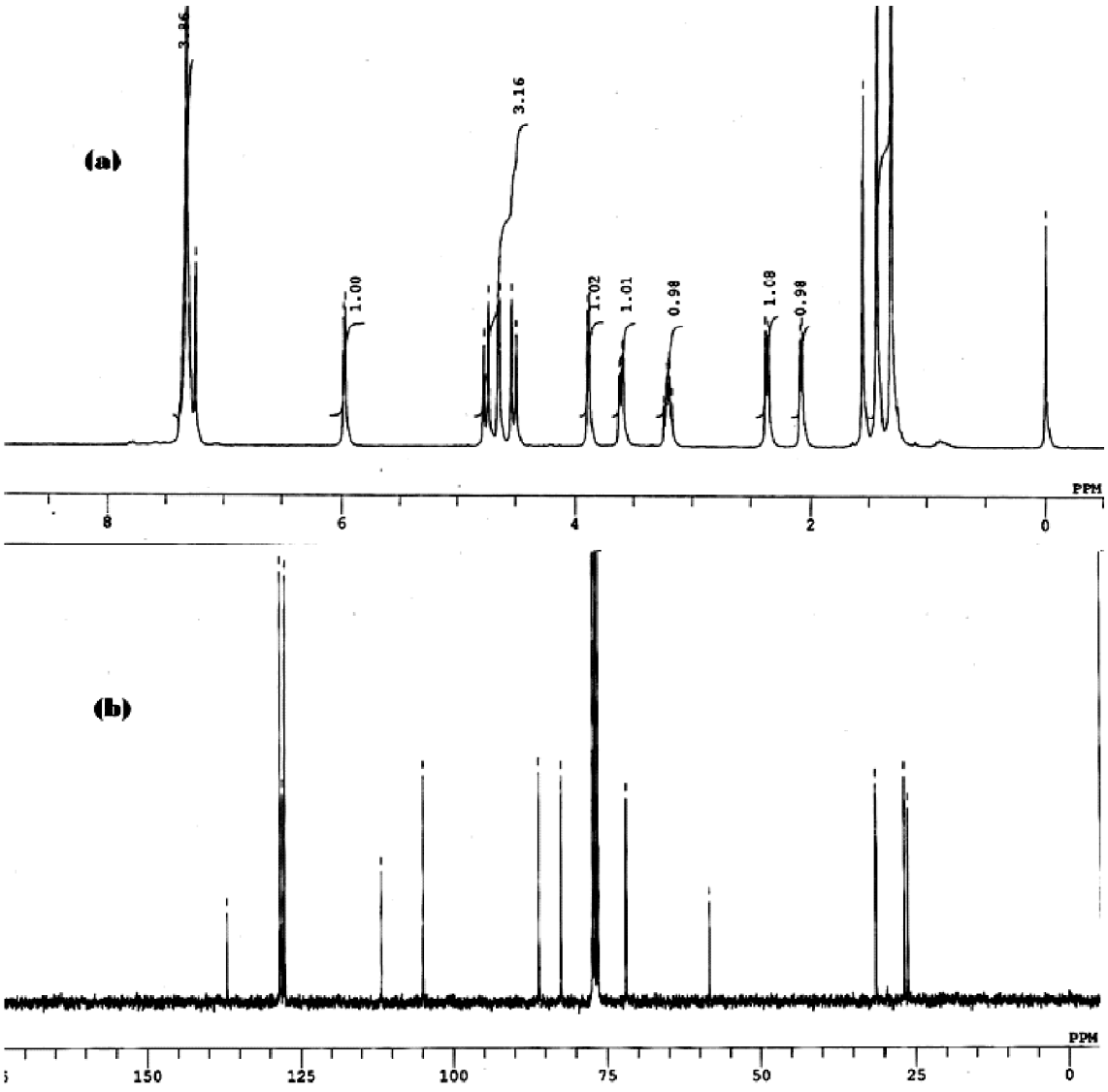


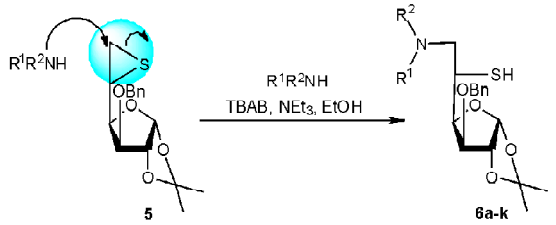
Fig. 2. (a) ^{1}H NMR (300 MHz, $CDCl_3$) and (b) ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of thiirane **5**.

zyl-1,2-*O*-isopropylidene-xylofuranos-5-thiiranes **5** was obtained by reacting it with TBAB in anhydrous ethanol at refluxing temperature for 18–24 h (Scheme 2).

The nucleophilic ring opening of thiirane with various amines including primary, secondary, heterocyclic, glycosyl as well as diamine is the key step of this methodology which is driven by TBAB; a phase transfer catalyst in ethanolic medium. The regioselective ring opening of thiirane **5** by some of the selected primary and secondary amines in ethanol was poor even under refluxing condition and reaction could not reach to the completion. To overcome this problem, we evaluated a number of bases and to our pleasant surprise, the reaction proceeded satisfactory on aid of triethyl amine and starting material was consumed completely within 24 h on refluxing. The combination of triethyl amine (NEt_3) as a base and TBAB as phase transfer catalyst was revealed for the complete consumption of starting materials. Thus, under the optimized reaction condition, thiirane **5** on reaction with primary amines as well as secondary amines in presence of NEt_3 and TBAB in anhydrous alcohol at refluxing afforded corresponding glycosylated aminothiols (**6a-k**) in quantitative yield via regioselective thiirane ring opening (Table 1). The progress of reaction was monitored on TLC (on 60 F-254 silica) and desired glycosyl aminothiols were isolated by column chromatography (SiO_2) using a gradient of chloroform and methanol as eluent. The structures of all the compounds were elucidated on the basis of their spectroscopic data including ^{1}H NMR, ^{13}C NMR, IR and MS.

Likewise, the secondary amines namely *N*-pyridylpiprazine, morpholine and glycosyl amine on similar reaction with thiirane **5** gave corresponding glycofuronosylated aminothiols in almost quantitative yields. We further explored the library with some selective heterocyclic and glycosyl amines to make the diversity in glycosyl aminothiol. On the

Table 1. Glycosyl aminothiols **6a-k** synthesized from glycosyl thiirane **5** via Scheme **2**[a]



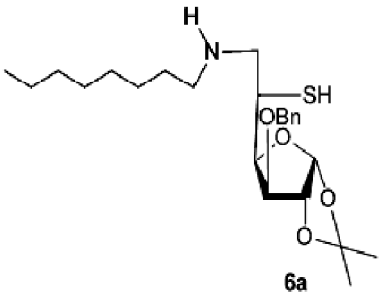
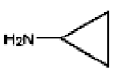
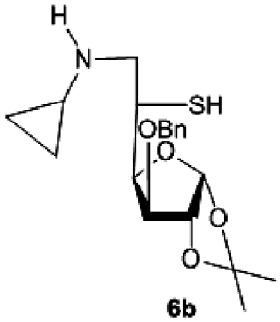
Entry	R^1R^2NH	Reaction product (**6a-k**)	Yield (%)
1			84
2			85

Table-1 (contd.)

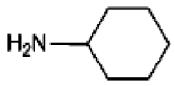
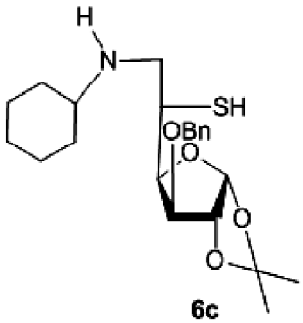
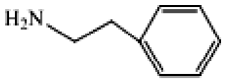
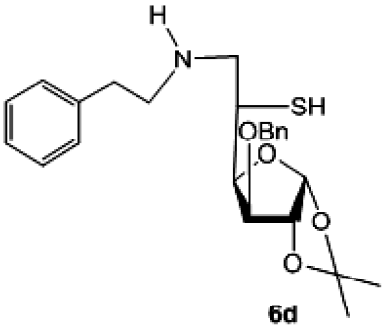
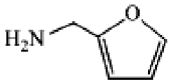
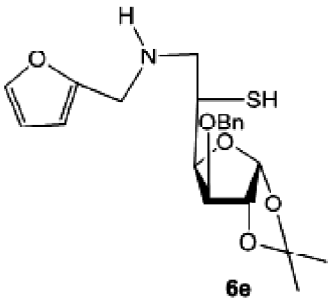
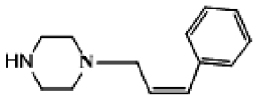
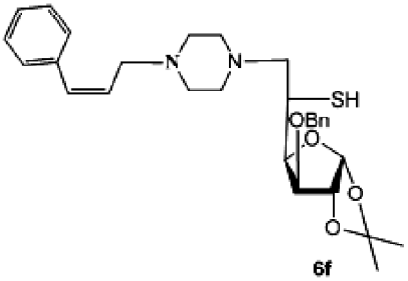
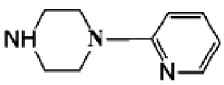
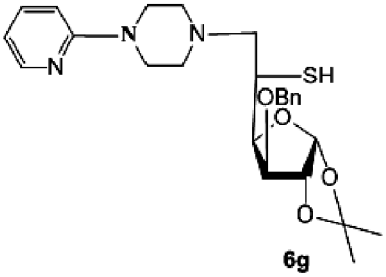
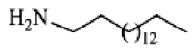
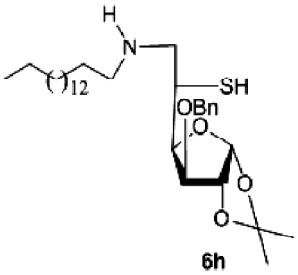
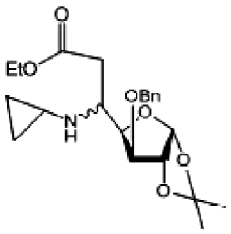
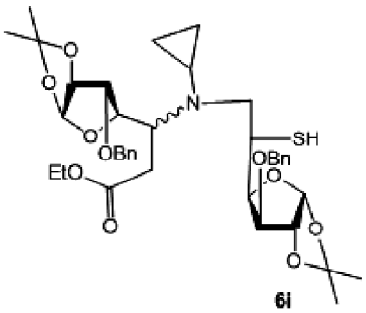
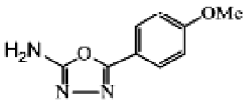
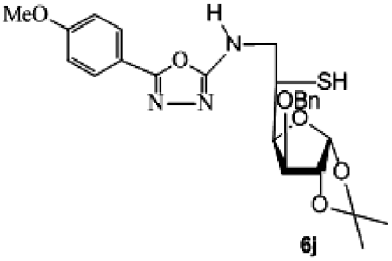
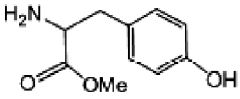
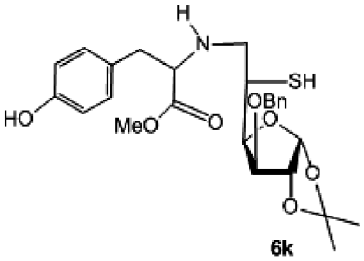
3		 **6c**	80
4		 **6d**	83
5		 **6e**	85
6		 **6f**	90
7		 **6g**	82

Table-1 (contd.)

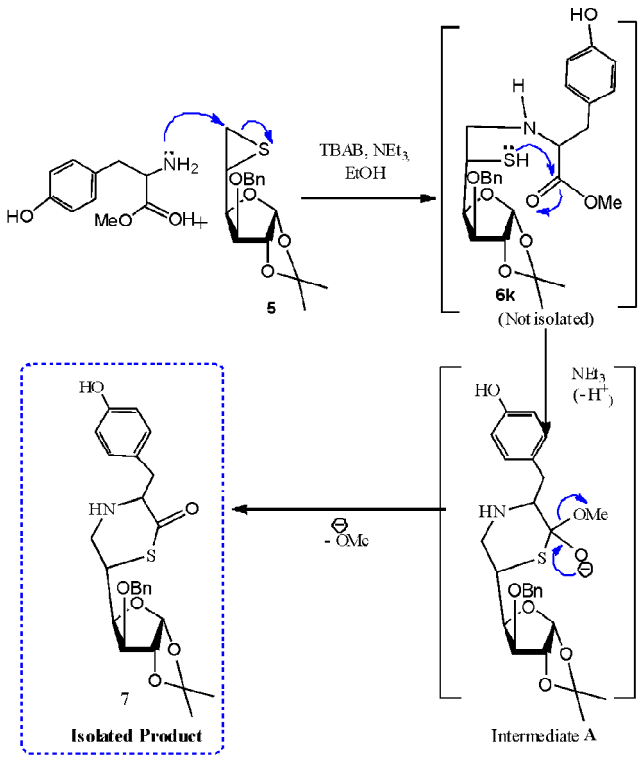
8		 **6h**	85
9		 **6i**	~5[b]
10		 **6j**	~ 5[b]
11		 **6k**	Cyclization led to **7** (87%)

Molar ratios: Compound **5** (1.0 equiv.), amine (1.2 equiv.), base NEt_3 (0.4 ml), TBAB (0.5 equiv.), ethanol (10 mL), reaction temperature: r.t. to 80°C, reaction time: 18–24 h. [a]Yields reported after purification by column chromatography (SiO_2). [b]Reaction temperature: 120°C

other hand, reaction of 3-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl] and ethyl{3-*O*-benzyl-5,6-dideoxy-5-cyclopropylamino-1,2-*O*-isopropylidene}-β-L-ido-heptofuranuronates with glycosylated thiirane **5** under the similar reaction conditions could not show remarkable progress. The major amount of starting materials remained unreacted (as evident from TLC) and only a little conversion to respective product (5%) was noticed under refluxing condition, where we could not successfully isolate the target compound in pure form.

Further to introduce the diversity in the glycosyl aminothiol, we treated glycosyl thiirane **5** with tyrosine methyl ester under the similar optimized conditions and the product obtained

was evaluated for its NMR (^{1}H and ^{13}C NMR). To our surprise, NMR and mass data were not in accordance with the result expected as there was no peak corresponding to methyl protons of methoxy group (OCH_3) in ^{1}H NMR spectrum as well OCH_3 signal in ^{13}C NMR spectrum. Further, in MS spectrum appearance of base peak at *m/z* = 494 (M+Na) confirmed for the formation of cyclised product. The data supported the formation of a six-membered thiomorpholinone ring **7** in 86% yield which is due to the nucleophilic attack of lone pair electrons of sulphur in compound **6k** facilitating the expulsion of methoxide anion via intermediate **A** (Scheme 3). This compound may verify to be interesting with respect to its promising biological activity.

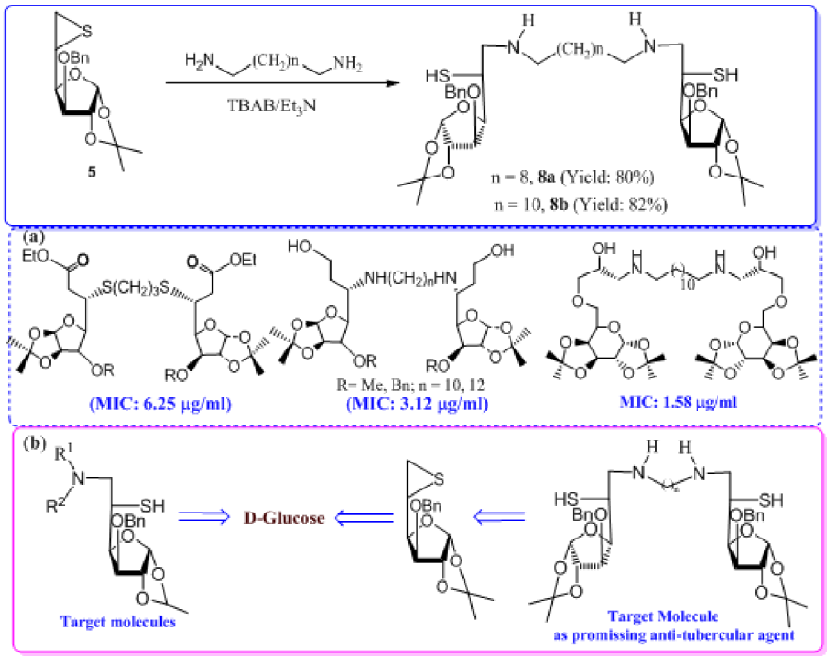


Scheme 3. Synthesis of 3-glycosylated-(4-hydroxybenzyl)-6-methylthiomorpholin-2-one (**7**) from glycosylated thiirane **5**.

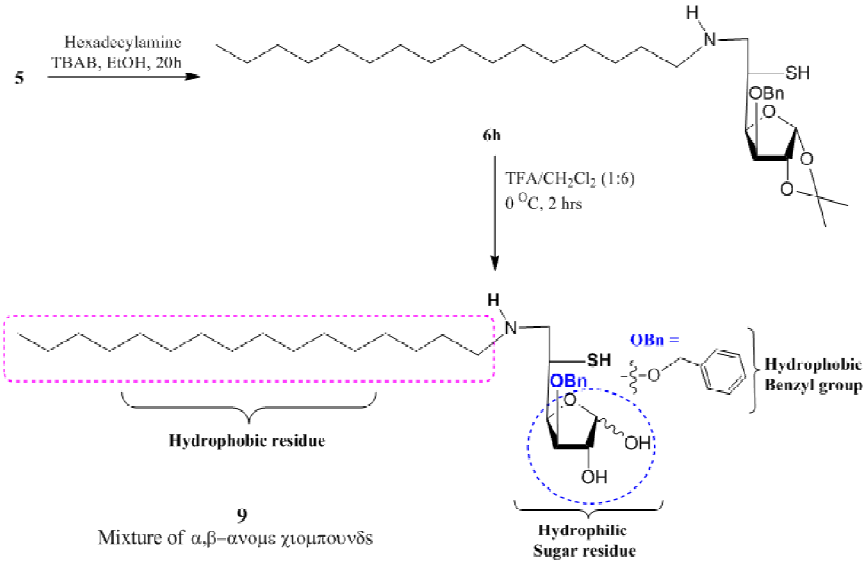
Furthermore, towards the synthesis of N^1,N^{12}-bis-(3-*O*-benzyl-5(*S*)-hydroxymethyl-5,6-dideoxy-6-hydroxyl-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)-1,12-diaminododecane (**8a**), we pursued the same procedure. Thus, the reaction of thiirane **5** separately with 1,10-diamino decane or 1,12-diamino dodecane under similar reaction condition afforded the respective N^1,N^n-diglycofuranosylated amino alcohol **8a** or **8b** in good yield via regioselective ring opening of thiirane ring (Scheme 4).

In a particular example, the treatment of compound **5** with 1,10-diaminodecane in presence of NEt_3/TBAB in ethanol under optimized reaction condition afforded compound **8a** in 80% yield. Structure of the developed molecule was ascertained on the basis of its ^{1}H NMR, ^{13}C NMR, IR and MS spectrum. Our previously synthesised N_1,N_n-bis-galactopyranosyl aminoalcohols showed potent activity against *M. tuberculosis* H_{37}Rv *in vitro* and displayed activity in MDR TB and found to be superior to ethambutol, a clinically used anti-TB drug in *in vitro* screening[21]. Also, a series of N_1,N_n-xylofuranosylated diaminoalkanes, obtained through 1,4-conjugate addition of diamines to glycosylated olefinic ester[23] followed by LAH reduction have shown promising anti-tubercular activities[24] and it was envisaged to inhibit arabinosyl transferase, a crucial enzyme involves in cell wall biosynthesis[25]. Developed diaminothiols **8a,b** contain the -NH and -SH groups separated by two carbon atoms in these molecules thus closely resemble with the structure of anti-TB drug ethambutol with thiol group instead of alcoholic group. These resulted compounds having structural similarity with known anti-TB aminoalcohols is envisaged to hold promise for effective anti-tubercular activities.

In addition to their immense medicinal perspectives, carbohydrate containing molecules have also been gaining attention due to their widespread applications in surfactant industry as renewable raw materials[26]. The development of carbohydrate-based surfactant for the exclusive use of natural resource by utilizing the cheap and easily available simple carbohydrate for example, D-glucose may be considered a high priority area. Recently, Adam *et al.* reported synthesis and photo controllable ice recrystallization inhibition (IRI) activity of a series of carbohydrate based surfactants[27]. Compared to some standard products, carbohydrate-based surfactant has notable advantages including improved performance, environmental compatibility as well as reduced health issues of consumers, etc.[28,29]. Thus, glycosylated aminothiol **6h** obtained in 85% yield by reacting thioepoxide with hexadecyl amine was further subjected to isopropylidene deprotection in order to make it hydrophilic residue. This designed molecule **9** is non-ionic surfactant prepared from D-



Scheme 4. Synthesis of N^1,N^n-bis-glycosylated diaminothiols (**8a, b)** from glycosyl thiirane (**5**).



Scheme 5. Synthesis of glycosyl aminothiol contains both the hydrophilic carbohydrate moiety and hydrophobic long chain hydrocarbon residue to serve as promising candidate to exhibit surface-active properties.

glucose as renewable raw material and a long chain hexadecyl amine residue (Scheme 5). Since, this aminothiol contains both the hydrophilic carbohydrate moiety and hydrophobic long chain hydrocarbon residue, thus it can serve a promising candidate to exhibit surface-active properties. Research and future aspects are being explored in this particular field in our laboratory.

Conclusions

In summary, a series of novel glycosylaled β-aminothiols has been successfully developed from the respective glycosyl thiirane using a simple and economical protocol. The resulting compounds were obtained in excellent yield with great ease via TBAB-catalyzed ring opening of the thiirane ring with a variety of primary and secondary amines including

aliphatic, aromatic, heterocyclic and sugar-based amines. Glycosyl thiirane on reaction with tyrosine methyl ester under the similar optimized condition underwent consecutive cyclization and led to the formation of respective thiomorpholinone ring. Similar reactions with diamines led to the corresponding di-glycosyl N_1,N_n-diaminothiols in good yields. Furthermore, glycosylated aminothiol developed from D-glucose as renewable raw material contains both the hydrophilic carbohydrate moiety and also hydrophobic long chain hexadecyl amine residue thus can serve a promising candidate to exhibit surface-active properties for designing non-ionic surfactant. The developed glycosylated β-aminothiols may serve as promising chemotherapeutic potential for the drug development against tuberculosis.

Experimental

General:

For few of the described synthesis, glass wares were dried over an open flame before use in connection with an inert atmosphere (N_2). Solvents were evaporated under reduced pressure at temperature <50°C. Thin layer chromatography (TLC) was performed using silica gel 60 F-254 plates with I_2 vapors as detecting agent followed by spraying with Draggendorff reagent. Silica gel (230–400 mesh) was used for column chromatography. TMS (0.0 ppm) was used as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. Infrared spectra were recorded as KBr pellets by a Perkin-Elmer RX-1 spectrometer. Unless otherwise stated, all materials were obtained from commercial suppliers, Sigma-Aldrich, SRL, and Spectrochem. Pvt. Ltd., and were used without further purification.

*1,2-O-Isopropylidene-5,6-anhydro-3-O-benzyl-xylofuranos-5-episulphide (**5**):*

To a solution of glycosyl epoxide **(4**, 2.5 g, 8.56 mmol) in MeOH (25 mL), thiourea (0.92 g, 12.1 mmol) was added fraction-wise at 0°C and the reaction was allowed to stir for 10 min and then the stirring was continued for 12 h at room temperature. Progress of the reaction was monitored by TLC (ethyl acetate/*n*-hexane, 1:9 ratio). Solvent was evaporated under reduced pressure and the residue was extracted with ethyl acetate (2×100 mL). The organic layer was washed with water (2×10 mL), then with brine solution (10 ml) and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure (below 55°C) and column chromatography (SiO_2) of crude product using gradient mixtures of *n*-hexane/ethyl acetate (8:1 to 6:1) afforded the desired compound **5** (1.91 g, yield 73%) as an oil. MS: *m/z* 209 (M +H$^+$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H, Ar-H), 5.98 (d, *J* 3.0 Hz, 1H, H-1), 4.78 (d, *J* 14.7 Hz, 1H, -OCH_APh), 4.66 (d, *J* 3.0 Hz, 1H, H-2), 4.54 (d, *J* 14.7 Hz, 1H, -OCH_BPh), 3.89 (d, *J* 3.3 Hz, 1H, H-4), 3.62 (m, 1H, H-3), 3.22 (m, 1H, H-5), 2.38 (dd, *J* 13.8, 2.7 Hz, 1H, H-6$_A$), 2.09 (m, 1H, H-6$_B$), 1.43–1.31 [s, 6H, 2×CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.19, 128.51, 128.09, 127.72 (Ar-*C*), 111.76 (>*C*$(CH_3)_2$), 104.95 (*C*-1), 82.13 (C-2), 82.58 (C-4), 82.52 (*C*-3), 71.98 (O*C*H_2Ph), 58.420 (C-5), 31.39 (C-6), 26.76 and 26.24 (2×CH_3) ppm.

*General experimental procedure for the synthesis of glycosylated aminothiols (**6a-k**):*

To a stirred solution of compound **5** (1.0 equiv.) in ethanol (10 mL), amine was added (1.2 equiv.) then triethylamine (0.4 ml) and tetra butyl ammonium bromide (0.1 g) were added in fraction-wise and stirring was continued for 15 min at room temperature. Then, the reaction was allowed to refluxed at 80°C for 18–24 h (progress of the reaction was monitored by TLC). Once after completion of the reaction (confirmed by TLC, chloroform/methanol, 98:2 as solvent system), the solvent was evaporated under reduced pressure (<55°C). Crude mass was extracted with CH_2Cl_2 (2×100 ml), washed with H_2O (10 ml), dried over anhydrous Na_2SO_4 and then solvent was evaporated under reduced pressure (>55°C). The residue thus obtained was subjected to column chromatography (SiO_2) using a gradient mixtures of chloroform/methanol (98:2) to afford the respective glycosylated aminothiol (**6a-k**) as diastereomeric mixture.

*3-O-Benzyl-5-octylamino-5,6-dideoxy-6-sulphydryl-1,2-O-isopropylidene-β-L-ido-furanose (**6a**):*

Compound **5**(0.2 g, 0.65 mmol) on treatment with octylamine (0.17 g, 1.31 mmol), triethylamine (0.4 ml), TBAB (100 mg, 0.31 mmol), in anhydrous ethanol (10 ml) at 80°C for 18 h and workup followed by column chromatography (chloroform/methanol, 98:2 ratio) as described in general procedure afforded compound **6a** as colourless oil. Yield: 84%; MS: *m/z* 460 (M+Na); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 5H, Ar-H), 5.88 (d, *J* 3.9 Hz, 1H, H-1), 4.68 (d, *J* 11.7 Hz, 1H, -OCH_APh), 4.61 (d, *J* 3.6 Hz, 1H, H-2), 4.47 (d, *J* 11.7 Hz, 1H, -OCH_BPh), 3.92 (m, 1H, H-4), 3.45 (m, 2H, H-

3 and H-5), 2.79 and 2.70 (dd, *J* 13.8 Hz and 2.7 Hz, 1H, H-6_A), 2.62 (m, 3H, H-6_B and $NHCH_2$), 2.11 (bs, 1H, NH), 1.48 (m, 2H, -$NHCH_2CH_2$),1.31–1.27 (s, 15H, 2×CH_3 and 10H, 5×CH_2), 0.88 (t, *J* 6.9 Hz, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.93, 128.37, 127.95, 127.79 (Ar-*C*), 111.49 (>*C*$(CH_3)_2$), 104.33 (*C*-1), 81.63 (C-2), 81.49 (C-4), 80.17 (*C*-3), 71.51 (OCH_2Ph), 51.03 (C-6), 49.41 (C-5), 48.56 (NCH_2), 31.76, 29.7 29.42, 29.20, 26.68, 22.57 (CH_2s) 27.22 and 26.24 (2×CH_3), 14.01 (NCH_2CH_3) ppm.

*3-O-Benzyl-5-cyclopropylamino-5,6-dideoxy-6-sulphydryl-1,2-O-isopropylidene-β-L-ido-furanose (**6b**):*

Compound **5** (0.2 g, 0.65 mmol) on treatment with cyclopropylamine (0.07 g, 1.22 mmol) triethylamine (0.4 ml), TBAB (100 mg, 0.31 mmol) in anhydrous ethanol (10 ml) at 80°C for 18 h and workup followed by column chromatography (chloroform/methanol; 98:2 as eluant) as described in general procedure afforded compound **6b** as colourless oil (yield 85%). MS: *m/z* 328 ($M+Na^+$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 5H, Ar-H), 5.92 (d, *J* 3.9 Hz, 1H, H-1), 4.71 (d, *J* 11.7 Hz, 1H, -OCH_APh), 4.61 (d, *J* 3.6 Hz, 1H, H-2), 4.48 (d, *J* 11.7 Hz, 1H, OCH_BPh), 3.89 (m, 1H, H-4), 3.42 (m, 2H, H-3 and H-5), 2.82 (m, 1H, H-6_A), 2.60 (m, 2H, H-6_B and NHCH), 1.78 (bs,1H, -NH), 1.47–1.31 (s, 6H, 2×CH_3), 0.45–0.32 (m, 4H, 2×CH_2 cyclopropyl ring-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.04, 128.34, 127.99, 127.79 (Ar-*C*), 110.63 (>*C*$(CH_3)_2$), 105.33 (*C*-1), 82.25 (C-2), 81.90 (C-4), 81.61 (*C*-3), 71.86 (OCH_2Ph), 56.49 (C-5), 48.49 (C-6), 30.40 (NCH), 27.25 and 26.21 (2×CH_3), 6.75 and 6.17 (2×CH_2) ppm.

*3-O-Benzyl-5-cyclohexylamino-5,6-dideoxy-6-sulphydryl-1,2-O-isopropylidene-β-L-ido-furanose (**6c**):*

Compound **5** (0.2 g, 0.65 mmol) on treatment with cyclohexylamine (0.09 g, 0.91 mmol), triethylamine (0.4 ml), TBAB (100 mg, 0.31 equiv.) in anhydrous ethanol (10 ml) at 80°C for 18–24 h and workup followed by column chromatography (chloroform/methanol; 98:2 as eluant) as described in general procedure afforded compound **6c** colourless oil. Yield 80%; MS: *m/z* 430 (M+Na); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7. 33 (m, 5H, Ar-H), 5.91 (bs, 2H, H-1 and OH), 4.63 (d, *J* 12 Hz, 1H, -OCH_APh), 4.50 (d, *J* 3.6 Hz, 1H, H-2), 4.43 (m, 1H, -OCH_BPh), 3.83 (m, 1H, H-4), 3.38 (m, 2H, H-3 and H-5), 2.75 (dd, *J* 13.2 Hz and 3.3 Hz, 1H, H-6_A), 2.66 (dd, *J* 13.2, 7.2 Hz, 1H, H-6_B), 2.40 (m, 1H, NHCH), 2.12–2.09 (m, 2H, 2×CH_2), 1.72 (m, 2H, 2×CH_2), 1.41–1.30 (s, 12H, 2×CH_3 and cyclohexyl ring-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.06, 128.38, 128.08, 127.93 (Ar-*C*), 111.09 (>*C*$(CH_3)_2$), 105.33 (*C*-1), 82.25 (C-2), 81.46 (C-4), 81.17 (*C*-3), 71.84 (OCH_2Ph), 58.49 (C-6), 48.67 (C-5), 31.20 (NCH), 32.22, 25.67, 24.83 and 24.47 (CH_2′s), 27.20 and 26.54 (2×CH_3) ppm.

*3-O-Benzyl-5-phenylethylamino-5,6-dideoxy-6-sulphydryl-1,2-O-isopropylidene-β-L-ido-furanose (**6d**):*

Compound **5 (**0.2 g, 0.65 mmol) on treatment with phenylethylamine (0.12 g, 0.99 mmol), triethylamine (0.4 ml), TBAB (100 mg, 0.31 equiv.) in anhydrous ethanol (10 ml) at 80°C for 18–24 h and workup followed by column chromatography (chloroform/methanol; 98:2 as eluant) as described in general procedure afforded compound **6d** as colourless oil. Yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.20 (m, 10H, 2×Ar-H), 5.89 (d, *J* 3.3 Hz, 1H, H-1), 4.67 (d, *J* 12 Hz, 1H, -OCH_APh), 4.60 (d, *J* 3.6 Hz, 1H, H-2), 4.48 (d, *J* 11.7 Hz, 1H, OCH_BPh), 3.95–3.33 (m, 3H, H-4, H-3 and H-5), 3.98 (m, 2H), 3.05 (dd, *J* 13.8, 2.7 Hz, 1H, H-6_A), 2.88 (dd, *J* 13.2, 7.2 Hz, 1H, H-6_B), 2.07 (b, 2H, NH and OH), 1.30–1.25 (s, 6H, 2×CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.78 (Ar-qC), 137.95 (Ar-qC), 128.62, 128.46 128.39, 127.90, 127.70, 126.09 (Ar-*C*), 111.59 (>*C*$(CH_3)_2$), 105.07 (*C*-1), 82.25 (C-2), 81.78 (C-4), 81.61 (*C*-3), 72.22 (OCH_2Ph), 56.42 (C-6), 50.89 (CH_2Ph), 50.49 (C-5), 36.17 (NCH_2), 27.22 and 26.65 (2×CH_3) ppm.

*3-O-Benzyl-5-frfurylethylamino-5,6-dideoxy-6-suphydryl-1,2-O-isopropylidene-β-L-ido-furanose (**6e**):*

Compound **5** (0.2 g, 0.65 mmol) on treatment with furfurylamine (0.1 g, 1.03 mmol), triethylamine (0.4 ml), TBAB (100 mg, 0.31 equiv.) in anhydrous ethanol (10 ml) at 80°C for 18–24 h and workup followed by column chromatography (chloroform/methanol; 98:2 as eluant) as described in general procedure afforded compound **6e** as colourless oil. Yield 85%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 6H, 5 Ar-H and 1 Furfuryl-*H*), 6.20–6.11 (m, 2 Furfuryl-*H*) 5.90 (d, *J* 3.6 Hz, 1H, H-1), 4.66 (d, *J* 11.7 Hz, 1H, -OCH_APh), 4.56 (d, *J* 3.3 Hz, 1H, H-2), 4.48 (d, *J* 11.7 Hz, 1H, -OCH_BPh), 4.11–3.54 (m, 3H, H-4, H-3 and H-5), 3.75 (s, 2H, NCH_2), 2.73 (m, 1H, H-6_A), 2.62 (m, 2H, NH and H-6_B), 1.41–1.23 (s, 6H, 2×CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.22 (Furfury-qC), 147.45 (Furfuryl-CH), 137.48, 128.23, 127.87, 127.47 (Ar-*C*), 111.63 (>*C*$(CH_3)_2$), 108.95 and 106.90 (Furfury-CH), 104.42 (*C*-1), 82.45 (C-2), 81.96 (C-4), 81.69 (*C*-3), 72.01 (OCH_2Ph), 52.72 (C-6), 50.49 (C-5), 45.93 (NCH_2), 27.56

and 26.33 (2×CH_3) ppm.

*3-O-Benzyl-5-cinnamilpiprazine-5,6-dideoxy-6-suphydryl-1,2-O-isopropylidene-β-L-ido-furanose (**6f**)*:

Compound **5** (0.5 g, 1.62 mmol) on treatment with cinnamilpiprazine (0.47 g, 2.32 mmol), triethylamine (0.4 ml), TBAB (100 mg, 0.31 equiv.) in anhydrous ethanol (10 ml) at 80°C for 18–24 h and workup followed by column chromatography (chloroform/methanol; 98:2 as eluant) as described in general procedure afforded compound **6f** as colourless oil. Yield = 90%; R_f 0.52; MS: *m/z* 533 (M+Na); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.21 (m, 10H, Ar-H), 6.48 (d, 1H, PhCH), 6.25 (m, 1H, PhCH=C*H*), 5.86 (d, *J* 3.6 Hz, 1H, H-1), 4.63 (d, *J* 11.7 Hz, 1H, -OCH_APh), 4.57 (m, 1H, H-2), 4.49 (d, *J* 11.4 Hz, 1H, -OCH_BPh), 4.21 (m, 1H, H-4), 3.90 (m, 1H, H-3), 3.37 (m, 1H, H-5), 3.06 (m, 3H, NCH_2 and H-6$_A$), 2.38–2.54 (m, 10H, CH_2 and H-6$_B$), 2.38 (broad multiplet, 9H, D_2O exchangeable SH and 4×NCH_2), 1.48–1.29 (s, 6H, 2×CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3 (Pyridyl-qC), 147.90 (Pyridyl-CH), 137.63 (Pyridyl-CH), 137.47, 128.45, 127.87, 127.71 (Ar-*C*), 113.32 (Pyridyl-CH), 111.63 (>*C*(CH_3)$_2$), 107.00 (Pyridyl-CH), 105.12 (*C*-1), 82.25 (C-2), 81.90 (C-4), 81.61 (*C*-3), 72.26 (O*C*H_2Ph), 63.68 (C-6), 61.73 (C-5), 45.22 (N*C*H_2), 26.75 and 26.21 (2×CH_3) ppm.

*3-O-Benzyl-5-pyridylpiprazine-5,6-dideoxy-6-sulphydryl-1,2-O-isopropylidene-β-L-ido-furanose (**6g**)*:

Compound **5** (0.2 g, 0.65 mmol) on treatment with *N*-pyridylpiprazine (0.26 g,1.59 mmol), triethylamine (0.4 ml), TBAB (100 mg, 0.31 equiv.) in anhydrous ethanol (10 ml) at 80°C for 18 h and workup followed by column chromatography (chloroform/methanol; 98:2 as eluant) as described in general procedure afforded compound **6g** as colourless oil. Yield 82%; MS: *m/z* 472 (M+H$^+$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, *J* 3.9 Hz, 1H, Pyridyl-H), 7.78 (t, *J* 7.2, 1H, Pyridyl-H), 7.35 (m, 5H, Ar-H), 6.52 (m, 2H, Pyridyl-H), 5.90 (d, *J* 3.3 Hz, 1H, H-1), 4.69 (d, *J* 11.7 Hz, 1H, -OCH_APh), 4.56 (m, 2H, H-2 and -OCH_BPh), 4.48 (d, *J* 11.7 Hz, 1H, -OCH_BPh), 3.23 (m, 1H, H-4), 3.98 (m, 1H, H-3), 3. 41 (m, 5H, H-5 and 2×CH_2), 2.69–2.57 (m, 3H, CH_2 and H-6$_A$), 2.52–2.38 (m, 3H, CH_2 and H-6$_B$), 1.49–1.31 (s, 6H, 2×CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.39 (Pyridyl-qC), 147.87 (Pyridyl-CH), 137.23 (Pyridyl-CH), 136.99, 128.47, 127.89, 127.54 (Ar-*C*), 113.01 (Pyridyl-CH), 111.66 (>*C*(CH_3)$_2$), 107.00 (Pyridyl-CH), 105.02 (*C*-1), 82.20 (C-2), 81.91 (C-4), 81.61 (*C*-3), 72.22 (O*C*H_2Ph), 58.06 (C-5), 48.16 (C-5), 53.32, 45.22 (NCH_2), 26.75 and 26.21 (2×CH_3) ppm.

*3-O-Benzyl-5-hexadecylamino-5,6-dideoxy-6-sulphydryl-1,2-O-isopropylidene-β-L-ido-furanose (**6h**)*:

Compound **5** (0.3 g, 0.97 mmol) on treatment with hexadecylamine (0.32 g, 1.94 mmol), triethylamine (0.4 ml), TBAB (100 mg, 0.31 equiv.) in anhydrous ethanol (15 ml) at 80°C for 18 h and workup followed by column chromatography (chloroform/methanol; 98:2 as eluant) as described in general procedure afforded compound **6h** as colourless oil. Yield 85%; MS: *m/z* 572 (M+Na); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 5H, Ar-H), 5.83 (m, 2H, H-1 and OH), 4.71 (d, *J* 11.7 Hz, 1H, -OCH_APh), 4.63 (d, *J* 3.6 Hz, 1H, H-2), 4.56 (d, *J* 11.7 Hz, 1H, -OCH_BPh), 4.10 (m, 1H, H-4), 3.86 (m, 2H, H-3), 3.20 (m, 1H, H-5), 2.38 (m, 4H, H-6$_A$, H-6$_B$ and NHCH_2), 2.31 (bs, 1H, NH), 1.46–1.27 (s, 34H, 2×CH_3 and 14×CH_2), 0.87 (t, *J* 6.9 Hz, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.59, 128.48, 128.13, 127.72 (Ar-*C*), 111.52 (>*C*(CH_3)$_2$), 104.63 (*C*-1), 82.25 (C-2), 81.58 (C-4), 80.18 (*C*-3), 71.84 (O*C*H_2Ph), 51.03 (C-6), 49.57 (C-5), 46.25 (NCH_2), 31.89, 29.69 29.33, 26.65, 26.80, 26.45, 22.65 (CH_2s), 27.37 and 26.33 (2×CH_3), 14.09 (NCH_2CH_3) ppm.

Isopropylidene group in compound **6h** was removed successfully by treating this compound with trifluoro acetic acid (TFA) in dichloromethane (1:6, v/v) at 0°C for 2 h and led to the formation of diol **9**, which is now mixture of two anomers and we couldn't isolated them in the pure form.

*3-O-Benzyl-5-[ethyl{3-O-benzyl-5,6-dideoxy-5-cyclopropylamino-1,2-O-isopropylidene}-α-D-gluco and β-L-ido-heptofuranuronates]-5,6-dideoxy-6-suphydryl-1,2-O-isopropylidene-β-L-ido-furanose (**6i**)*:

A solution of compound **5** (0.2 g, 0.65 mmol) and ethyl {3-*O*-benzyl-5,6-dideoxy-5-cyclopropylamino-1,2-*O*-isopropylidene}-α-D-gluco and β-*L*-ido-heptofuranuronate (0.4 g, 0.97 mmol) in ethanol was magnetically stirred. Then added triethylamine (0.4 ml) and tetra butyl ammonium bromide (0.01 g, 0.31 equiv.) in the reaction and then reflux the stirring solution for 18 h. The solvent was evaporated under reduced pressure but the yield is not more than 5% and the compound could not be separated successfully.

*3-O-Benzyl-5-3-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]-5,6-dideoxy-6-sulphydryl-1,2-O-isopropylidene-α-D-glucofuranose (**6j**)*:

A solution of compound **5** (0.32 g, 1.03 mmol) and 3-[5-

(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl] (0.3 g, 1.57 mmol) in ethanol was magnetically stirred. Then added triethylamine (0.5 ml) and tetra butyl ammonium bromide (0.01 g, 0.31 equiv.) in the reaction and then reflux the stirring solution for overnight. The solvent was evaporated under reduced pressure but the reaction yield is not satisfactory (not more than 5%) and so in this case too we were unable to isolate the desired compound as it is contaminated with starting material.

*3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-β-L-idofuranose-(4′-hydroxybenzyl)-6′-methylthiomorpholin-2′-one (**7**):*

Compound **5** (0.2 g, 0.65 mmol) on treatment with tyrosinemethylester (0.25 g, 1.28 mmol), triethylamine (0.4 ml), TBAB (100 mg, 0.31 equiv.) in anhydrous ethanol (10 ml) at 80°C for 20 h and workup followed by column chromatography (chloroform/methanol; 98:2 as eluant) as described in general procedure afforded the respective cyclised compound **7** as colourless oil. Yield 86%; MS: *m/z* 494 (M+Na); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 5H, Ar-H), 6.98 (d, *J* 8.4, 2H, Ar-H), 6.74 (d, *J* 8.4, 2H, Ar-H) 5.87 (d, *J* 3.3 Hz, 1H, H-1), 4.61 (d, *J* 12.0 Hz, 1H, -OCH_APh), 4.55 (m, 2H, 1H, H-2) 4.46 (d, *J* 11.7 Hz, 1H, -OCH_BPh), 4.24 (m, 1H, H-4), 4.06 (t, 1H, NCH), 3.95 (m, 2H, H-3), 3.57 (s, 3H, OCH_3), 3.20 (m, 1H, H-5), 2.89–2.76 (m, 4H, H-6 and $PhCH_2$), 3.04–2.83 (m, 3H, 1H, H-6_A, 2H, $PhCH_2$), 2.55 (m, 1H, H-6_B), 1.78 (bs, 1H, NH), 1.48–1.29 (s, 6H, 2×CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.33 (C=O), 154.85 (ArC-OH), 137.13, 130.24, 130.19, 128.44, 127.90, 127.85, 127.76, 115.89 (Ar-*C*), 111.58 (>*C*$(CH_3)_2$), 104.48 (*C*-1), 81.76 (C-2), 81.66 (C-4), 80.27 (*C*-3), 71.58 (OCH_2Ph), 62.69 (OCH_3), 60.73 (C-6), 51.71 (C-5), 46.58 (NCH), 38.18 (Ph-CH), 26.61 and 26.20 (2×CH_3) ppm.

*N^1,N^{12}-Bis-(3-O-benzyl-5(S)-hydroxymethyl-5,6-dideoxy-6-sulphydryl-1,2-O-isopropylidene-a-D-xylofuranos-5-yl)-1,12-diaminododecane (**8**):*

Compound **5** (0.5 g, 1.62 mmol) on treatment with 1,12-dodecyldiamine (0.16 g, 0.81 mmol), triethylamine (0.4 ml), TBAB (200 mg, 0.62 equiv.) in anhydrous ethanol (15 ml) at 80°C for 18 h and workup followed by column chromatography (chloroform/methanol; 98:2 as eluant) as described in general procedure afforded compound **8b** as major isomer as colourless oil (Yield 82%); MS: *m/z* 663 ($M+H^+$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 10H, Ar-H), 5.85 (d, *J* 3.9 Hz, 1H, H-1), 4.71 (d, *J* 11.7 Hz, 1H, -OCH_APh), 4.64 (d, *J* 3.6 Hz, 1H, H-2), 4.54 (d, *J* 11.7 Hz, 1H, -OCH_BPh), 4.21 (m, 3H, H-4, H-3 and H-5), 3.16 (m, 1H, H-6_A), 2.88 (m, 3H, H-6_B and $NHCH_2$), 1.80 (b, 2H, NH and OH), 1.47 (m, 2H, $NHCH_2CH_2$), 1.29–1.27 (s, 34H, 2×CH_3 and 14×CH_2), 0.89 (t, *J* 6.9 Hz, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 137.42 (ArC), 128.5, 128.2, 128.0 (Ar-C), 111.78 (>C$(CH_3)_2$), 104.49 (C-1), 82.06 (C-2), 81.97 (C-4), 81.47 (C-3), 72.56 (-OCH_2Ph), 65.45 (C-6), 58.85 (C-5), 49.05 (NCH_2), 29.47, 29.19, 27.79, 27.23, 26.86 (CH_2's), 26.72 and 26.19 [2× >C$(CH_3)_2$] ppm.

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