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Synthesis of guanidino sugar conjugates as GlcβArg analogs

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Abstract The β-glucosyl linkage to the guanidine group of arginine (Arg) is found in amylogenin, a glycoprotein from sweet corn. Such a linkage is formed by a rare *N*-glycosylation of proteins. Synthesis of analogs of the unusual *N*-glycosidic linkage (GlcβArg) with an acetamido or triazole spacer between the glycosyl residue and the guanidine moiety was accomplished by the reaction of fully acetylated sugar unit containing a free amino group with bis-Boc-thiourea. Synthesis of *N*-glucosylarginine with an amido linker was also achieved during the present study. This methodology was also extended to the synthesis of cationic glucolipid.

Keywords *N*-Glycoprotein · Linkage region analogs · Guanidine · Arginine

Introduction

Guanidines are highly basic molecules [1] which interact with functional groups present in enzymes or receptors on the basis of hydrogen bonds and electrostatic interactions. A wide range of natural guanidine derivatives have been isolated from microorganisms, terrestrial invertebrates, marine and terrestrial vertebrates, marine sponges and freshwater organisms as well as higher plants [2]. Some synthetic guanidine compounds act as β-secretase inhibitors [3], inhibitors of Na^+/H^+ exchanger [4], and chemotherapeutic agents such as anticancer [5], antiviral [6] and antiparasitic [7]. Guanidine-linked sugar compounds also have a wide range of biological activities such as antibacterial [8], antidiabetic [9], inhibitors of enzymes including thrombin, glycosidases [10, 11], and nitric oxide synthases [12]. Due to their inimitable biological activity, these guanidine containing compounds are noteworthy targets for drug design and discovery. Guanidine is also present in *N*-glycoprotein linkage region of a self glycosylating amylogenin protein isolated from sweet corn where glucose is β-linked to guanidino group of arginine (GlcβArg) [13, 14]. There are a few literature reports which deal with the synthesis of 1-(*N*ω-L-arginino)-1-deoxy-β-D-glucose (GlcβArg) [15] and related guanidine sugar conjugates [16–19]. In addition, previous studies showed that β-D-glucopyranosyl bismethoxyphosphoramidate [20, 21], *N*-azidoacetyl-β-D-glucopyranosylamine [22] and 4-phenyl-*N*-(β-D-glucopyranosyl)-1H-1,2,3-triazole-1-acetamide [23] could be exploited as leads for antidiabetic agents by applying the structure-based ligand design approach on glycogen phosphorylase b (GPb). In the present work, we have designed *N*-(β-D-glycopyranosyl)guanidinoacetamides as potential inhibitors of GPb. Amide-1,2,3-triazole bioisosterism in the case of glycogen phosphorylase inhibition is already demonstrated [24–26]. It would be very worthwhile to prepare the 1-(β-D-glycosyl)-4-guanidinomethyl-[1,2,3]-triazole analogs of GlcβArg linkage with triazole as a linker. Synthesis of *N*-glucosylarginine with an amido linker as an analog of the naturally occurring GlcβArg linkage and synthesis of cationic glucolipid is also planned.

Results and discussion

Our novel design, which is biomimetic in nature, is based on the GlcβArg linkage with a spacer between the glycosyl residue and the guanidine moiety. Two types of spacers, acetamido and triazole moieties were chosen which may increase the binding affinity of these compounds to the target

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enzyme. Various guanidinylating reagents are reported in the literature for the synthesis of guanidine containing compounds [27]. The synthetic method employed in the present work involves, as a key step, the reaction of fully acetylated sugar unit containing a free amino group with bis-Boc-thiourea or with suitably functionalized S-methyl-bis-Boc-isothiourea.

Synthesis of *N*-(β-D-glycosyl)guanidinoacetamides (3 & 4)

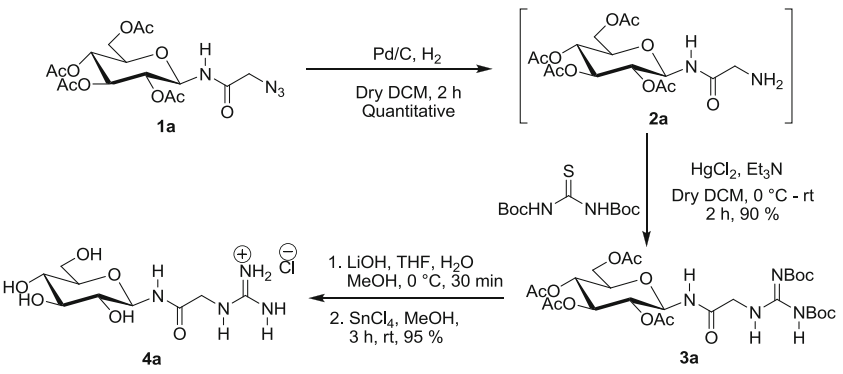
We have planned the synthesis of glycosyl guanidinoacetamides starting from per-*O*-acetylated glycosyl azidoacetamides (**1a**–**1f**) and bis-Boc-thiourea [28]. Glycosyl azidoacetamides (**1a**–**1f**) were prepared from fully acetylated glycosyl azides using the method developed earlier in our laboratory [29]. Glucosyl azidoacetamide **1a** was reduced to the corresponding aminoacetamide **2a** using $Pd/C/H_2$ in dry dichloromethane. Aminoacetamide **2a** was reacted with bis-Boc-thiourea, triethylamine and mercuric chloride at 0 °C to afford the product **3a** in very good yield (Scheme 1). This methodology was extended to other glycosyl azidoacetamides (**1b**–**1f**) derived from Gal, GlcNAc, Man, Xyl and Lac. The yields of the products (**3b**–**3f**) obtained are presented in Table 1. All the products were characterized based on the physical and spectral data including IR, ^{1}H, ^{13}C-NMR and ESI-MS. In the IR spectra of compounds **3a**–**3f**, there are characteristic absorption bands of guanidinyl group around 1620 cm^{-1}. The ^{1}H-NMR spectra displayed three –NH proton signals. The most downfield –NH signal appearing around 11.35 ppm as a singlet is assignable to –NHBoc proton. A triplet resonating around 8.88 ppm corresponds to $–CH_2NH–$ proton due to coupling with the adjacent methylene protons. The amide –NH proton signal was observed around 7.00 ppm as a doublet with a coupling constant of 9.6 Hz. ^{13}C-NMR spectra showed the guanidine carbon signal around 156.0 ppm.

Fully protected glycopyranosyl guanidinoacetamides derived from Glc, Gal and GlcNAc (**3a**–**3c**) were taken up for de-*O*-acetylation using LiOH (0.05 M) at −10 °C. The Boc groups were removed by treatment with $SnCl_4$ in methanol at room temperature (Scheme 1) to give the hydrochloride salt of glycopyranosyl guanidinoacetamides (**4a**–**4c**) in fairly good yield. In the ^{13}C-NMR spectra amidocarbonyl carbon signal and guanidino carbon signals were seen around 171.0 ppm and 157.5 ppm, respectively.

Synthesis of fully protected 1-(β-D-glycosyl)-4-guanidinomethyl-[1,2,3]-triazoles (10a-10f)

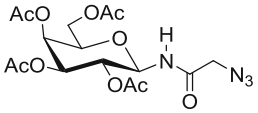
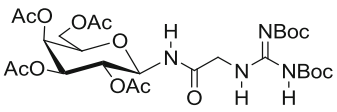
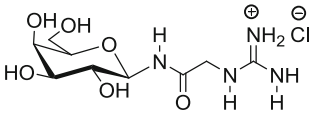
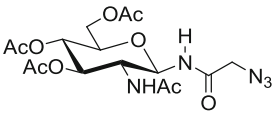
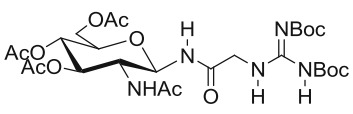
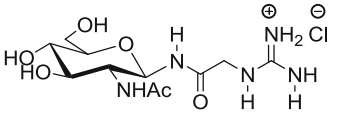
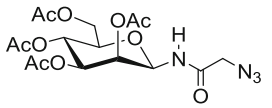
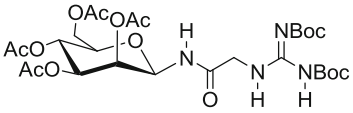
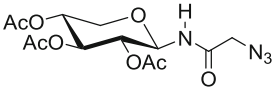
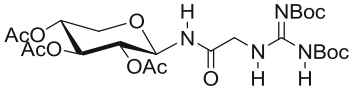
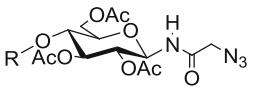
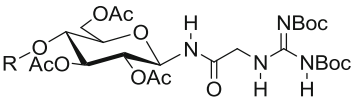
Per-*O*-acetylated glycosyl azidomethyltriazoles (**8a**–**8f**) and bis-Boc-thiourea were chosen as starting material. Fully acetylated glycosyl azidomethyltriazoles (**8a**–**8f**) were prepared from the glycosyl azides (**5a**-**5f**) by using literature procedure [30] (Scheme 2, Table 2). Hitherto unknown xylosyl hydroxymethyltriazole **6e** and azidomethyltriazoles derived from Gal, Xyl and Lac (**8b**, **8e** & **8f**) were fully characterized based on physical and spectral methods.

Azidomethyltriazoles (**8a**–**8f**) were reduced by using $SnCl_2.2H_2O/Sn$ resulting in the formation of per-*O*-acetylated glycosyl aminomethyltriazoles (**9a**–**9f**). These were coupled with bis-Boc-thiourea under the same reaction conditions as used for compounds **3a**–**3f** leading to the formation of products **10a**–**10f** in good to excellent yield (Scheme 2, Table 2). All the products were characterized based on the physical and spectral data including ^{1}H, ^{13}C-NMR and ESI-MS. Similar to compounds **3a**–**3f**, the characteristic absorption band for guanidinyl group was seen around 1620 cm^{-1}. The ^{1}H-NMR spectrum displayed two –NH proton signals. –NHBoc proton appeared as a singlet ~11.44 ppm. A triplet resonating around 8.75 ppm corresponds to $–CH_2NH–$ proton due to coupling with adjacent methylene protons. Methine proton (H-5′) of triazole ring appeared around 7.75 ppm as a singlet. In the ^{13}C-NMR spectrum, triazole carbon signals were seen around 143.0 (C4′) and 121.0 (C5′) ppm. The 1,4-regioisomeric nature of these compounds was established by the large and positive difference [Δ(δC4-δC5)] in the ^{13}C chemical shifts, 143.0 and 121.0 ppm of C4′ and C5′, respectively, as has been observed earlier in other triazole-linked compounds prepared by click reaction [31]. The guanidino carbon signal was observed around 156.0 ppm.



Scheme 1 Synthesis of hydrochloride salt of *N*-(β-D-glucosyl)guanidinoacetamide (**4a**)

Table 1 List of glycosyl guanidinoacetamides synthesized

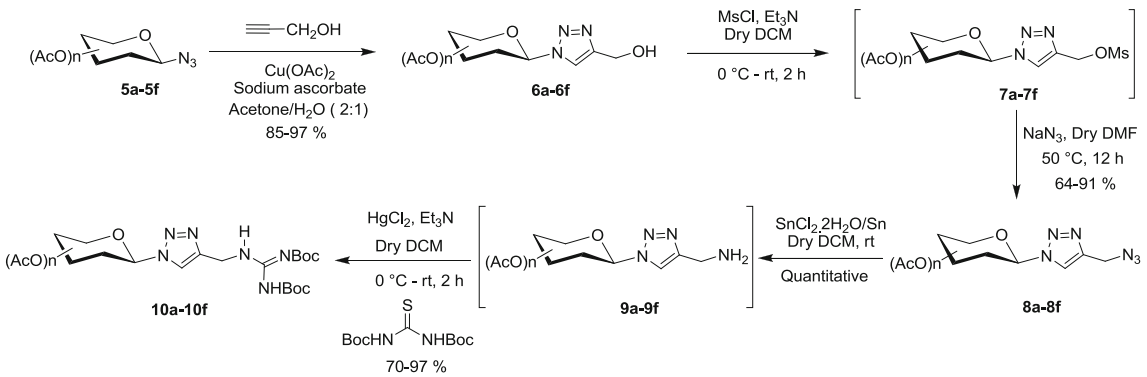
Sr. No.	Per-*O*-acetylated glycosyl azidoacetamide	Fully protected glycosyl guanidinoacetamide	Yield[a] (%)	Deprotected glycosyl guanidinoacetamide	Yield (%)
1	 (**1b**)	 (**3b**)	95	 (**4b**)	93
2	 (**1c**)	 (**3c**)	85	 (**4c**)	80
3	 (**1d**)	 (**3d**)	70	-	
4	 (**1e**)	 (**3e**)	50	-	
5[b]	 (**1f**)	 (**3f**)	88	-	

[a] Yield of isolated pure product

[b] R = β-Gal

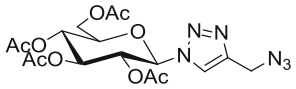
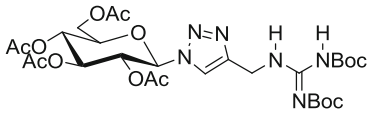
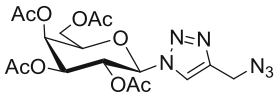
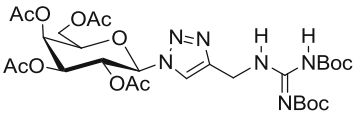
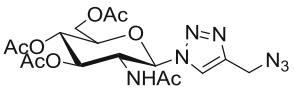
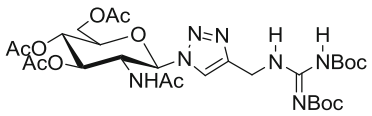
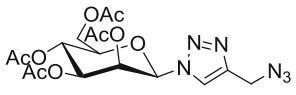
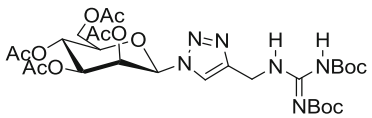
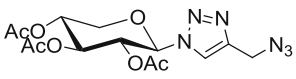
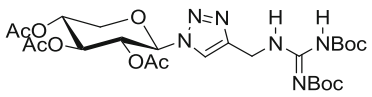
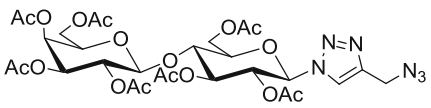
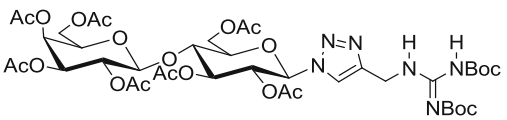
Synthesis of *N*-glucosylarginine with an amido linker (12)

In order to synthesize compound **12**, 5-[*N*′*N*″-bis(*tert*-butoxycarbonyl)-S-methylisothiourea]-*N*′-[(2(*S*)-2-benzyloxycarbonylamino]valeric acid benzyl ester (**11**) and aminoacetamide **2a** were used as synthons. Compound **11** was prepared by the alkylation of *N*′,*N*″-bis(*tert*-butoxycarbonyl)-S-methylisothiourea [32] with 2(*S*)-2-(benzyloxycarbonylamino)-5-iodovaleric acid benzyl ester [33] using NaH as a base in dry DMF solvent (Scheme 3). The target molecule **12** was prepared in 52 % yield by refluxing a solution of compound **11** and aminoacetamide **2a** in dry THF for 2 days (Scheme 3). Product was fully characterized based on the physical and spectral data including ^{1}H, ^{13}C-NMR and ESI-MS.



Scheme 2 Synthesis of fully protected 1-(β-D-glycosyl)-4-guanidinomethyl-[1,2,3]-triazoles (**10a**–**10f**)

Table 2 List of per-*O*-acetylated glycosyl azidomethyltriazoles and fully protected 1-(β-D-glycosyl)-4-guanidinomethyl-[1,2,3]-triazoles synthesized

Sr. No.	Glycosyl azidomethyltriazole	Yield[a] (%)	Glycosyl guanidinomethyltriazole	Yield (%)
1.	 (**8a**)	95	 (**10a**)	92
2.	 (**8b**)	78	 (**10b**)	86
3.	 (**8c**)	79	 (**10c**)	95
4.	 (**8d**)	78	 (**10d**)	90
5.	 (**8e**)	84	 (**10e**)	70
6.	 (**8f**)	54	 (**10f**)	94

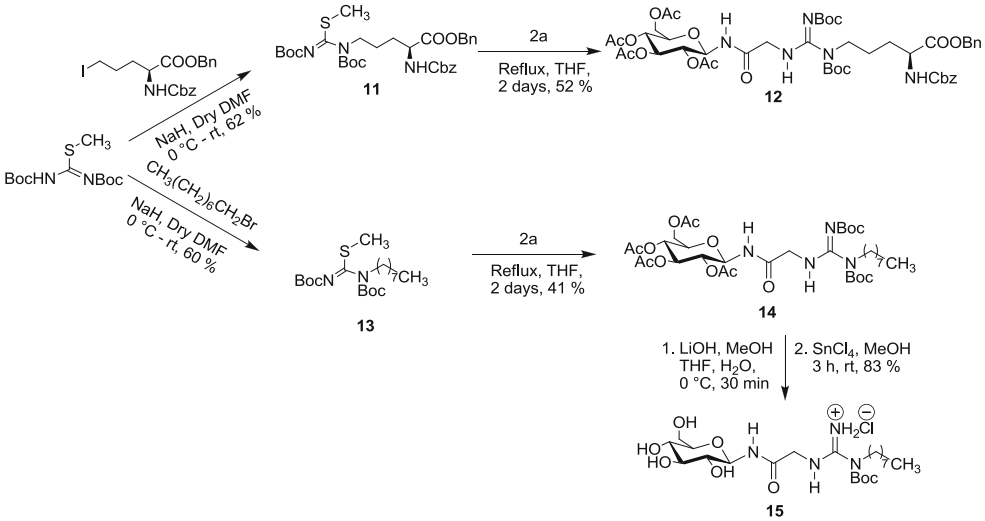
[a] Starting from glycosyl azide

Synthesis of hydrochloride salt of *N*-(β-D-glucopyranosyl)-*N*′-(*n*-octyl)guanidinoacetamide (15)

After establishing the validity of this approach for the preparation of the *N*-glucosylarginine, the methodology was further applied to the preparation of cationic glucolipid. Cationic liposomes containing various covalently grafted cell specific ligands are capable of delivering their genetic payloads to specific body cells. Galactose has been used in the polar head group region of liver-specific cationic glycolipid [34]. Cationic glucolipid (**15**) was prepared in which conjugation of sugar moiety to the lipophilic chain was done by using guanidinoacetamido group as a linker. Aminoacetamide **2a** and *N*′-(*n*-octyl)-*N*′,*N*″-bis(*tert*-butoxycarbonyl)-S-methylisothiourea (**13**) were used as synthons. Compound **13** was prepared by *N*-alkylation of *N*′,*N*″-bis(*tert*-butoxycarbonyl)-S-methylisothiourea with octyl bromide using sodium hydride as a base in dry DMF solvent (Scheme 3).

Guanidinoacetamido derivative (**14**) was prepared by refluxing a solution of aminoacetamide **2a** with compound **13** in THF for 2 days (Scheme 3). Column chromatography of the crude product over silica gel afforded the required product (**14**) in 41 % yield. Deprotection of compound **14** was performed under the same reaction conditions as used for compounds **3a**-**3c** to give the hydrochloride salt of *N*-(β-D-glucopyranosyl)-*N*′-(*n*-octyl)-guanidinoacetamide (**15**) in 83 % yield. The free guanidino lipid (**15**) has been fully characterized by both physical and spectral methods. The ^{13}C-NMR spectrum displayed the amidocarbonyl carbon

Scheme 3 Synthesis of *N*-glucosylarginine with an amido linker (**12**) and hydrochloride salt of *N*-(β-D-glucopyranosyl)-*N*′-(*n*-octyl)-guanidinoacetamide (**15**)



signal at 171.0 ppm and guanidino carbon resonated at 156.2 ppm.

Summary and conclusions

Guanidines have great biochemical and pharmaceutical significance. Several sugar guanidine conjugates have been synthesized in the present work as novel analogs of GlcβArg linkage. Synthetic methodology involved the reaction of glycosyl aminoacetamides with bis-Boc-thiourea to give the respective guanidine derivatives in good to excellent yields. The same methodology was utilized for the synthesis of triazole containing guanidino sugar derivatives derived from the per-*O*-acetylated glycosyl aminomethyltriazoles. Synthesis and characterization of *N*-glucosylarginine with an amido linker as analog of the naturally occurring GlcβArg linkage was also performed. This method was also used for the synthesis of hydrochloride salt of *N*-(β-D-glucopyranosyl)-*N*′-(*n*-octyl)guanidinoacetamide. All the 18 guanidine sugar conjugates (**3a**–**3f**, **4a**–**4c**, **10a**–**10f**, **12**, **14** and **15**) synthesized during the present work are hitherto unknown in literature and were characterized completely. These compounds may have great potential as inhibitors of various enzymes such as glycogen phosphorylase (Preliminary results showed that compound **4a**-Scheme 1 exhibits an IC_{50} value of 168±5.7 μM (Dr. ED Chrysina, personal communication), glycosidases and glycosyltransferases.

Experimental section

General

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. All solvents employed were of commercial grade, purified by distillation and dried according to standard procedures. The dried solvents were stored over 4 Å molecular sieves. All the sugars used were purchased from the Sigma-Aldrich, USA or Carbosynth Limited, UK and used as such without further purification. Thin layer chromatograms were performed on 25 mm E. Merck silica gel plates (60 F-254). Detection was done by dipping into puncal solution. Column chromatography was performed using silica gel (100–200 mesh). Optical rotation was measured at 25 °C on a JASCO-DIP 200 digital polarimeter using a cell of 10 mm length. NMR spectra were recorded on a BRUKER AV 400 spectrometer using tetramethylsilane (TMS) as an internal standard for those spectra that were run in $CDCl_3$. D_2O was also used as the solvent with no internal reference. Chemical shift values are expressed in parts per million (ppm) and the coupling constants in Hertz (Hz). High-resolution ESI-MS analyses were performed with Micromass Q-Tof mass spectrometer in the positive ion mode.

General procedure for the synthesis of per-*O*-acetylated *N*-(β-D-glycosyl)-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidinoacetamide (3a-3f)

Per-*O*-acetylated glycosyl azidoacetamide (**1a**–**1f**) (0.5–1.04 g, 1.5 mmol) was reduced to the corresponding aminoacetamide (**2a**–**2f**) using Pd/C (10 % by weight) under H_2 atmosphere in dry CH_2Cl_2 (5 mL). After the disappearance of azidoacetamide, the reaction mixture was filtered through celite bed to remove Pd/C and was concentrated to syrup. The bis-Boc-thiourea (276 mg, 1 mmol), aminoacetamide (365–761 mg, 1.1 mmol) and triethylamine (0.28 mL, 2.0 mmol) were dissolved in dry CH_2Cl_2 (5 mL) at room temperature. The mixture was cooled in an ice bath. Mercuric chloride (353 mg, 1.3 mmol) was added and the mixture was stirred for 20 min,

before it was warmed to RT. After the disappearance of starting material (bis-Boc-thiourea) based on TLC, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and filtered through celite. The filtrate was washed with water (15 mL) and aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to dryness on a rotoevaporator. The residue obtained was purified by column chromatography over silica gel (100–200 mesh) using a mixture of ethyl acetate and hexane to afford the product (**3a**–**3f**) as a solid in good to excellent yield.

N-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidinoacetamide (3a)

Column chromatography with 32 % AcOEt-hexane afforded **3a** (582 mg, 90 %) as a white solid; mp 104–106 °C; $[\alpha]_D^{25}$ -19.9° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3335, 2979, 2938, 2362, 1756, 1643, 1619, 1556, 1415, 1370, 1311, 1228, 1145, 1095, 1041, 980, 907, 809, 775; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.36 (s, 1H, –NHBoc), 8.84 (t, 1H, –CH_2NH–), 7.28 (d, 1H, *J*=9.6 Hz, –NH1), 5.29 (t, 1H, *J*=9.6 Hz, H-3), 5.22 (t, 1H, *J*= 9.6 Hz, H-1), 5.06 (t, 1H, *J*=9.6 Hz, H-4), 4.91 (t, 1H, *J*= 9.6 Hz, H-2), 4.30 (dd, 1H, *J*=4.4 & 12.8 Hz, H-6a), 4.17–4.01 (m, 3H, –CH_2NH– & H-6b), 3.84–3.78 (m, 1H, H-5), 2.08, 2.03, 2.01 (3 s, 12H, 4 x –$COCH_3$), 1.51 (s, 18H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.7, 170.6, 169.9, 169.6, 169.3 (4 x –$COCH_3$ & –NH$COCH_2$–), 163.0, 156.3, 153.0, 83.6, 79.7, 78.3 (C-1), 73.7 (C-5), 72.9 (C-3), 70.5 (C-2), 68.3 (C-4), 61.8 (C-6), 44.7 (–CH_2NH–), 28.4, 28.3, 28.1, 20.7, 20.6, 20.5 (4 x –$COCH_3$); ESI-MS: calcd for $C_{27}H_{43}N_4O_{14}$ ($[M+H]^+$): 647.2776, found: 647.2768.

N-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidinoacetamide (3b)

Column chromatography with 36 % AcOEt-hexane afforded **3b** (614 mg, 95 %) as a white fluffy powder; mp: 110 °C; $[\alpha]_D^{25}$ +11.0° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3335, 2979, 2935, 1754, 1644, 1619, 1551, 1415, 1395, 1370, 1310, 1227, 1145, 1086, 1058; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.38 (s, 1H, –NHBoc), 8.88 (t, 1H, –CH_2NH–), 7.23 (d, 1H, *J*=8.8 Hz, –NH1), 5.44 (d, 1H, *J*=2.8 Hz, H-4), 5.21 (t, 1H, *J*=8.8 Hz, H−1), 5.16–5.05 (m, 2H, H-2 & H-3), 4.18–4.00 (m, 5H, H-5, H-6a, H-6b & –CH_2NH–), 2.15, 2.05, 2.02, 1.99 (4 s, 12H, 4 x –$COCH_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.0, 170.4, 170.1, 169.8, 169.2 (4 x –$COCH_3$ &–NH$COCH_2$–), 162.9, 156.3, 152.9, 83.6, 79.6, 78.6 (C-1), 72.5, 70.9, 68.1, 67.3 (C-4), 61.2 (C-6), 44.6 (–CH_2NH–), 29.7, 28.3, 28.0, 28.0, 20.7, 20.6, 20.5 (4 x–$COCH_3$); ESI-MS: calcd for $C_{27}H_{43}N_4O_{14}$ ($[M+H]^+$): 647.2776, found: 647.2769.

N-(2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl)-*N*′,*N*″-bis(*tert*-butoxycarbonyl) guanidinoacetamide (3c)

Column chromatography with 40 % AcOEt-hexane afforded **3c** (613 mg, 95 %) as a white solid; mp 124 °C; $[\alpha]_D^{25}$ -23.6° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3337, 3084, 2978, 2931, 1746, 1642, 1550, 1416, 1374, 1312, 1237, 1150, 1097, 1049; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.36 (s, 1H, –NHBoc), 8.89 (t, 1H, –CH_2NH–), 7.65 (d, 1H, *J*=8.0 Hz, –NH1), 6.06 (d, 1H, J= 8.0 Hz, –NH2), 5.15–5.01 (m, 3H, H-1, H-3 & H-4), 4.29 (dd, 1H, *J*=4.4 & 12.4 Hz, H-6a), 4.17–4.01 (m, 4H, H-2, H-6b,–CH_2NH–), 3.79–3.72 (m, 1H, H-5), 2.09, 2.05, 2.04, (3 s, 9H, 3 x–$COCH_3$), 1.91 (s, 3H, –NH$COCH_3$), 1.49 (s, 9H), 1.48 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.0, 171.8, 170.8, 169.7, 169.4 (3 x –$COCH_3$, –NH$COCH_3$ &–NH$COCH_2$–), 163.1, 156.2, 153.0, 83.5, 80.2 (C-1), 79.6, 73.6 (C-5), 73.0 (C-4), 68.0 (C-3), 61.9 (C-6), 53.1 (C-2), 44.3 (–CH_2NH–), 28.3, 28.1, 23.0 (–NH$COCH_3$), 20.8 (2C), 20.7 (3 x –$COCH_3$); ESI-MS: calcd for $C_{27}H_{44}N_5O_{13}$ ($[M+H]^+$): 646.2936, found: 646.2952.

N-(2,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranosyl)-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidinoacetamide (3d)

Column chromatography with 48 % AcOEt-hexane afforded **3d** (608 mg, 94 %) as a light yellow solid; mp 109–110 °C; $[\alpha]_D^{25}$ -8.9° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3330, 2979, 2936, 1755, 1646, 1618, 1559, 1541, 1413, 1370, 1309, 1227, 1146, 1102, 1057, 978, 906, 809, 775; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.37 (s, 1H, –NHBoc), 8.88 (t, 1H, –CH_2NH–), 6.79 (d, 1H, *J*= 9.2 Hz, –NH1), 5.54 (d, 1H, *J*=9.2 Hz, H-1), 5.35 (dd, 1H, *J*= 0.8 & 3.2 Hz, H-2), 5.22 (t, 1H, *J*=10.0 Hz, H-4), 5.11 (dd, 1H, *J*=3.2 & 10.0 Hz, H-3), 4.29 (dd, 1H, *J*=5.2 & 12.4 Hz, H-6a), 4.23–4.00 (m, 3H, –CH_2NH– & H-6b), 3.80–3.73 (m, 1H, H-5), 2.21, 2.10, 2.05, 1.98 (4 s, 12H, 4 x –$COCH_3$), 1.51 (s, 9H), 1.49 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.7, 170.2, 169.8, 169.7, 168.3 (4 x –$COCH_3$ & –NH$COCH_2$–), 163.0, 156.1, 152.8, 83.5, 79.6, 76.3 (C-1), 74.2 (C-5), 71.5 (C-3), 69.8 (C-2), 65.3 (C-4), 62.3 (C-6), 44.3 (–CH_2NH–), 28.2, 28.0, 20.8, 20.7 (2C), 20.5 (4 x –$COCH_3$). ESI-MS: calcd for $C_{27}H_{43}N_4O_{14}$ ($[M+H]^+$): 647.2776, found: 647.2751.

N-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)-*N*′,*N*″-bis (*tert*-butoxycarbonyl)guanidinoacetamide (3e)

Column chromatography with 44 % AcOEt-hexane afforded **3e** (403 mg, 70 %) as a white solid; mp 116 °C; $[\alpha]_D^{25}$ -4.2° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3433, 2979, 1758, 1731, 1643, 1619, 1558, 1417, 1393, 1369, 1312, 1227, 1145, 1092, 1069, 1037; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.37 (s, 1H, NHBoc), 8.86 (t, 1H, –CH_2NH–), 7.35 (d, 1H, –NH1), 5.29 (t, 1H, *J*= 9.6 Hz, H-3), 5.13 (t, 1H, *J*=9.6 Hz, H-1), 5.02–4.92 (m, 1H,

H-4), 4.86 (t, 1H, *J*=9.6 Hz, H-2), 4.15–4.02 (m, 3H, H-5a &–$C\underline{H}_2NH$–), 3.43 (t, 1H, H-5b), 2.04, 2.03, 2.02 (3 s, 9H, 3 x–$CO\underline{CH}_3$), 1.50 (s, 18H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.9, 170.0, 169.5 (3 x –$\underline{C}OCH_3$ & –$NH\underline{C}OCH_2$–), 163.0, 156.3, 153.0, 83.7, 79.8, 78.9 (C-1), 72.4 (C-3), 70.7 (C-2), 69.1 (C-4), 64.6 (C-5), 44.7 (–$\underline{C}H_2NH$–), 28.3, 28.1, 20.8, 20.7, 20.6 (3 x –$CO\underline{C}H_3$); ESI-MS: calcd for $C_{24}H_{39}N_4O_{12}$ ($[M+H]^+$): 575.2564, found: 575.2556.

N-[4-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl]-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidinoacetamide (3f)

Column chromatography with 60 % AcOEt-hexane afforded **3f** (739 mg, 79 %) as a yellow solid; mp 118–120 °C; $[\alpha]_D^{25}$ + 3.6° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3413, 3355, 2978, 2928, 2856, 1754, 1643, 1620, 1546, 1370, 1308, 1230, 1144, 1054; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.37 (s, 1H, –N$\underline{H}$Boc), 8.91 (t, 1H, –$CH_2N\underline{H}$–), 7.42 (d, 1H, *J*=8.4 Hz, –N$\underline{H}$1), 5.36 (d, 1H, *J*=2.4 Hz, H-4′), 5.29 (t, 1H, *J*=9.4 Hz, H-3), 5.21 (t, 1H, *J*=8.4 Hz, H-1), 5.10 (dd, 1H, H-2′), 4.96 (dd, 1H, H-3′), 4.85 (t, 1H, *J*=8.4 Hz, H-2), 4.55–4.38 (m, 2H, H-1′ & H6a′), 4.23–3.98 (m, 5H, –$C\underline{H}_2NH$–, H-6a, H-6b & H-6b′), 3.91 (m, 1H, H-4), 3.85–3.68 (m, 2H, H-5 & H-5′), 2.16, 2.13, 2.07, 2.05, 2.04, 2.01, 2.00 (7 s, 21H, 7 x –$CO\underline{C}H_3$), 1.51 (s, 9H), 1.49 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.9, 170.4, 170.2, 170.1, 169.5, 169.2, 169.1, (7 x –$\underline{C}OCH_3$ & –$NH\underline{C}OCH_2$–), 162.9, 156.2, 152.9, 100.9 (C-1′), 83.6, 79.7, 78.0 (C-1), 76.0 (C-5), 74.5 (C-5′), 72.5 (C-3), 71.0 (C-3′), 70.7 (C-2 & C-4), 69.0 (C-2′), 66.7 (C-4′), 62.1 (C-6′), 60.1 (C-6), 44.4 (–$\underline{C}H_2NH$–), 29.7, 28.2, 28.1, 28.0, 26.9, 20.9, 20.8, 20.7, 20.6 (2C), 20.5 (7 x –$CO\underline{C}H_3$); ESI-MS: calcd for $C_{39}H_{59}N_4O_{22}$ ($[M+H]^+$): 935.3621, found: 935.3641.

General procedure for the synthesis of hydrochloride salt of *N*-(β-D-glycopyranosyl)guanidinoacetamides (4a-4c)

Fully protected *N*-(β-D-glycopyranosyl)guanidinoacetamide (**3a**-**3c**) (646 mg, 1 mmol) was dissolved in a solution of 2.5:1.0:0.5 MeOH–H_2O–THF and cooled to −10 °C. LiOH (0.05 M, 6 equiv.) was added to this solution and the solution was stirred at 0 °C. After completion of the reaction based on TLC, the solution was diluted with water and the pH was adjusted to 3.0 with Amberlite IR-120 (H^+). The Amberlite was removed by filtration and MeOH & THF were removed under diminished pressure to obtain fully de-*O*-acetylated *N*-(β-D-glycopyranosyl)-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidinoacetamide. To a stirred solution of *N*-(β-D-glycopyranosyl)-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidinoacetamide (1 mmol) in MeOH was added stannic chloride (4 equiv). After 3 h of stirring at room temperature, TLC indicated the complete consumption of starting material. The solvent and excess of $SnCl_4$ were evaporated in vacuo. The remaining solid was dissolved in MeOH and ether was then added until the formation of a white precipitate of *N*-(β-D-glycopyranosyl)guanidinoacetamide.hydrochloride (**4a**–**4c**).

N-(β-D-Glucopyranosyl)guanidinoacetamide.hydrochloride (4a)

Yield=265 mg, 95 %; Colorless syrup; $[\alpha]_D^{25}$ -19.9° (c 1, H_2O); IR (Thin film, cm^{-1}): 3577, 3348, 2925, 1664, 1552, 1544, 1411, 1256, 1075, 1033; ^{1}H-NMR (400 MHz, D_2O): δ 5.05 (d, 1H, *J*=9.2 Hz, H-1), 4.15 & 4.10 (ABq, 2H, –$C\underline{H}_2NH$–), 3.91 (d, 1H, *J*=12.6 Hz, H-6a), 3.77 (dd, 1H, *J*= 5.2 Hz & 12.6 Hz, H-6b), 3.64–3.52 (m, 2H, H-3 & H-5), 3.51–3.40 (m, 2H, H-2 & H-4); ^{13}C-NMR (100 MHz, D_2O): δ 171.1 (–$NH\underline{C}OCH_2$–), 157.5, 79.3 (C-1), 77.6, 76.4, 71.7, 69.2, 60.5 (C-6), 43.8 (–$\underline{C}H_2NH$–); ESI-MS: calcd for $C_9H_{19}N_4O_6$ ($[M]^+$): 279.1305, found: 279.1305.

N-(β-D-Galactopyranosyl)guanidinoacetamide.hydrochloride (4b)

Yield=259 mg, 93 %; Colorless syrup; $[\alpha]_D^{25}$ +5.5° (c 1, H_2O); IR (Thin film, cm^{-1}): 3639, 3577, 3361, 2929, 2867, 1664, 1552, 1408, 1247, 1084, 1021; ^{1}H-NMR (400 MHz, D_2O): δ 4.91 (d, 1H, *J*=8.8 Hz, H-1), 4.05 & 4.01 (ABq, 2H,–$C\underline{H}_2NH$–), 3.91 (d, 1H, *J*=3.2 Hz, H-4), 3.76–3.70 (m, 1H, H-5), 3.69–3.62 (m, 3H, H-3, H-6a & H-6b), 3.58 (t, 1H, *J*=8.8 Hz, H-2); ^{13}C-NMR (100 MHz, D_2O): δ 171.1 (–$NH\underline{C}OCH_2$–), 157.3, 79.5 (C-1), 76.6 (C-5), 73.1 (C-3), 69.2 (C-2), 68.5 (C-4), 60.8 (C-6), 43.6 (–$\underline{C}H_2NH$–); ESI-MS: Calcd for $C_9H_{19}N_4O_6$ ($[M]^+$): 279.1305, found: 279.1310.

N-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)guanidinoacetamide.hydrochloride (4c)

Yield=256 mg, 80 %; Colorless syrup; $[\alpha]_D^{25}$ -7.2° (c 1, H_2O); IR (Thin film, cm^{-1}): 3295, 2942, 2453, 1740, 1665, 1539, 1394, 1226, 1182, 1096, 1058, 1033; ^{1}H-NMR (400 MHz, D_2O): δ 5.03 (d, 1H, *J*=9.6 Hz, H-1), 4.00 & 3.93 (ABq, 2H,–$C\underline{H}_2NH$–), 3.90–3.68 (m, 2H, H-2 & H-6a), 3.68 (dd, 1H, *J*=4.8 & 12.4 Hz, H-6b), 3.57 (t, 1H, *J*= 9.6 Hz, H-3), 3.52–3.35 (m, 2H, H-4 & H-5), 1.94 (s, 1H, –$NHCOC\underline{H}_3$); ^{13}C-NMR (100 MHz, D_2O): δ 174.8, 170.9 (–$NH\underline{C}OCH_3$ & –$NH\underline{C}OCH_2$–), 157.5, 78.6 (C-1), 77.6, 74.0, 69.5, 60.5, 54.1, 43.9, 22.1; ESI-MS: calcd for $C_{11}H_{22}N_5O_6$ ($[M]^+$): 320.1570, found: 320.1570.

General procedure for the synthesis of per-*O*-acetylated *N*-(β-D-glycosyl)-4-hydroxymethyl-[1,2,3]-triazoles (6a-6f)

To a vigorously stirred suspension of fully acetylated glycosyl azides (**5a**–**5f**) (0.9–1.98 g, 3 mmol) in acetone

(30 mL) was added propargyl alcohol (3.9 mmol). A solution of $CuSO_4.5H_2O$ (0.6 mmol) and sodium ascorbate (1.2 mmol) in distilled H_2O (2 mL) was added to the same reaction mixture. The reaction mixture was stirred vigorously at RT. After TLC (1:1 ethyl acetate/hexane) indicated completion of the reaction, water (30 mL) was added and the aqueous layer was extracted twice with CH_2Cl_2 (2 x 20 mL). The combined organic extract was washed with brine (15 mL), dried over Na_2SO_4, filtered, and evaporated to afford a crude solid residue, which was recrystallized from ethyl acetate and hexane to afford the pure product (**6a**-**6f**) as a solid. The data of **6a**–**6d** and **6f** have been previously reported [30, 35, 36]. The spectroscopic data of the new compound **6e** is listed below.

1-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)-4-hydroxymethyl-[1,2,3]-triazole (6e)

Yield=988 mg, 92 %; White solid; mp 158–160 °C; $[\alpha]_D^{25}$ -56.8° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3483, 1747, 1383, 1248, 1220, 1128, 1041, 1001; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H, H-5′), 5.79 (d, 1H, *J*=8.4 Hz, H-1), 5.47–5.32 (m, 2H, H-2 & H-3), 5.20–5.10 (m, 1H, H-4), 4.80 (br s, 2H, –C<u>H</u>$_2$OH), 4.30 (dd, 1H, *J*=5.6 & 11.6 Hz, H-5a), 3.60 (t, 1H, *J*=11.6 Hz, H-5b), 2.08, 2.06, 1.89 (3 s, 9H, 3 x –COC<u>H</u>$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.1, 170.0, 169.3 (3 x –<u>C</u>OCH$_3$) 150.0 (C4′), 120.5 (C5′), 86.3 (C-1), 72.2, 70.6, 68.4 (C-4), 65.5 (C-5), 55.9 (–<u>C</u>H$_2$OH), 20.5, 20.5, 20.1 (3 x –OCO<u>C</u>H$_3$); ESI-MS: calcd for $C_{14}H_{20}N_3O_8$ ($[M+H]^+$): 358.1250, found: 358.1235.

General procedure for the synthesis of per-*O*-acetylated 1-(β-D-glycosyl)-4-azidomethyl-[1,2,3]-triazoles (8a-8f)

To a solution of per-*O*-acetylated *N*-(β-D-glycosyl)-4-hydroxymethyltriazole (0.6–1.4 g , **6a**–**6f**) (2 mmol) in dry CH_2Cl_2 (5 mL) was added triethylamine (0.42 mL, 3.0 mmol) and methanesulfonyl chloride (0.18 mL, 2.4 mmol) at 0 °C and the reaction mixture was allowed to stir at RT under nitrogen. After the disappearance of starting material based on TLC, CH_2Cl_2 (25 mL) was added to it and the solution was washed with 1 N HCl (2×15 mL), saturated $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated to afford the mesylate as pale yellow oil. The crude mesylate (**7a**-**7f**) was dissolved in dry DMF (10 mL) and NaN_3 (5 equiv) was added. The mixture was warmed to 50 °C and stirred for 24 h. After completion of reaction based on TLC, DMF was removed under reduced pressure and CH_2Cl_2 (20 mL) was added. The extract was washed with distilled H_2O (2× 15 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated to afford the crude product as an off-white solid. Recrystallization from ethyl acetate and hexane afforded the azide (**8a**-**8f**) as an amorphous white solid. The data of **8a**, **8c** and **8d** have been previously reported [35]. The spectroscopic data of the new compounds **8b**, **8e** and **8f** are listed below.

1-(1,2,3,4-Tetra-*O*-acetyl-β-D-galactopyranosyl)-4-azidomethyl-[1,2,3]-triazole (8b)

Yield=801 mg, 84 %; White needle shaped crystal; mp 114–115 °C; $[\alpha]_D^{25}$ +0.9° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2098, 1751, 1457, 1370, 1223, 1159, 1112, 1084, 1061, 1047, 1019, 925; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 1H, H-5′), 5.86 (d, 1H, *J*=9.2 Hz, H-1), 5.59–5.51 (m, 2H, H-2 & H-3), 5.26 (dd, 1H, *J*=3.2 & 10.4 Hz, H-4), 4.51 (br s, 2H, –C<u>H</u>$_2$N$_3$), 4.27–4.11 (m, 3H, H-5, H-6a & H-6b), 2.23, 2.05, 2.02, 1.90 (4 s, 12H, 4 x –COC<u>H</u>$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.0, 169.7, 169.5, 168.8 (4 x–<u>C</u>OCH$_3$) 142.9 (C4′), 121.0 (C5′), 85.8 (C-1), 73.7 (C-5), 70.4 (C-4), 67.7, 66.8, 61.0 (C-6), 45.0 (–<u>C</u>H$_2$OH), 20.3, 20.1, 19.8 (4 x–CO<u>C</u>H$_3$); ESI-MS: calcd for $C_{17}H_{22}N_6O_9Na$ ($[M+Na]^+$): 477.1346, found: 477.1355.

1-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)-4-azidomethyl-[1,2,3]-triazole (8e)

Yield=737 mg, 91 %; White solid; mp 122 °C; $[\alpha]_D^{25}$ -56.0° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2101, 1753, 1462, 1376, 1321, 1249, 1233, 1079, 1043, 1013, 878; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H, H-5′), 5.80 (d, 1H, *J*= 8.8 Hz, H-1), 5.48–5.32 (m, 2H, H-2 & H-3), 5.21–5.11 (m, 1H, H-4), 4.49 (br s, 2H, –C<u>H</u>$_2$N$_3$), 4.36–4.26 (dd, 1H, *J*= 5.6 & 11.6 Hz, H-5a), 3.60 (t, 1H, *J*=11.6 Hz, H-5b), 2.08, 2.06, 1.89 (3 s, 9H, 3 x–COC<u>H</u>$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.0, 169.9, 169.1 (3 x–<u>C</u>OCH$_3$), 143.4 (C4′), 120.8 (C5′), 86.5 (C-1), 72.0 (C-3), 70.5 (C-2), 68.5 (C-4), 65.7 (C-5), 45.5 (–<u>C</u>H$_2$N$_3$), 20.7 (2C), 20.2 (3 x –CO<u>C</u>H$_3$); ESI-MS: calcd for $C_{14}H_{18}N_6O_7Na$ ($[M+Na]^+$): 405.1135, found: 405.1122.

1-[4-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl]-4-azidomethyl-[1,2,3]-triazole (8f)

Yield=980 mg, 64 %; White solid; mp 114 °C; $[\alpha]_D^{25}$ -13.8° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2103, 1752, 1433, 1372, 1227, 1173, 1130, 1112, 1085, 1046; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H, H-5″), 5.84 (d, 1H, *J*=8.8 Hz, H-1), 5.46–5.34 (m, 3H, H-2, H-3 & H-4′), 5.13 (dd, 1H, *J*=2.4 & 8.0 Hz, H-2′), 4.98 (dd, 1H, *J*=3.2 & 10.0 Hz, H-3′), 4.56–4.44 (m, 4H, H-1′, H-6a & –C<u>H</u>$_2$N$_3$), 4.20–4.05 (m, 3H), 4.00–3.94 (m, 3H), 2.17, 2.12, 2.08, 2.07, 2.06, 2.00, 1.88 (7 s, 21H, 7 x–COC<u>H</u>$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.3, 170.2, 170.1, 170.0, 169.4, 169.1, 169.0 (7 x–

COCH$_3$) 143.1 (C4″), 121.0 (C5″), 101.0 (C-1′), 85.4 (C-1), 75.9, 75.6, 72.4, 70.8, 70.7, 70.4, 69.0, 66.6, 61.7, 60.8, 45.3 (−CH$_2$N$_3$) 20.7, 20.6, 20.4, 20.1 (7 x –COCH$_3$); ESI-MS: calcd for $C_{29}H_{38}N_6O_{17}Na$ ([M+Na]$^+$): 765.2191, found: 765.2180.

General procedure for the synthesis of per-*O*-acetylated 1-(β-D-glycosyl)-4-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidinomethyl-[1,2,3]-triazoles (10a-10f)

Per-*O*-acetylated 1-(β-D-glycosyl)-4-azidomethyl-[1,2,3]-triazole (0.6–1.13 g, **8a**–**8f**) (1.5 mmol) was reduced to per-*O*-acetylated 1-(β-D-glycosyl)-4-aminomethyl-[1,2,3]-triazole (**9a**–**9f**) using $SnCl_2.2H_2O$/Sn in CH_2Cl_2. After the disappearance of starting material, the reaction mixture was filtered through celite bed and the filtrate was concentrated to syrup. Bis-Boc-thiourea (276 mg, 1 mmol), aminomethyltriazole (392–788 mg, 1.1 mmol) and triethylamine (0.28 mL, 2.0 mmol) were dissolved in CH_2Cl_2 (5 mL) at RT. The mixture was cooled in an ice bath. Mercuric chloride (353 mg, 1.3 mmol) was added and mixture was stirred for 20 min, before it was warmed to RT. The work-up of the product was carried out as described for compounds **3a**-**3f** to give the pure product (**10a**–**10f**) in good to excellent yield.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidinomethyl-[1,2,3]-triazole (10a)

Yield=637 mg, 95 %; White fluffy powder; mp 80 °C; $[\alpha]_D^{25}$ -10.6° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3337, 2979, 2938, 1758, 1643, 1619, 1568, 1457, 1418, 1370, 1320, 1228, 1134, 1093, 1059, 1039, 924, 808, 778; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.44 (s, 1H, –NHBoc), 8.77 (t, 1H, –CH$_2$NH–), 7.79 (s, 1H, H-5′), 5.87 (d, 1H, *J*=8.8 Hz, H-1), 5.43 (m, 2H, H-2 & H-3), 5.24 (t, 1H, *J*=10.0 Hz, H-4), 4.80–4.65 (m, 2H, –CH$_2$NH–), 4.30 (dd, 1H, *J*=5.2 & 12.8 Hz, H-6a), 4.15 (d, 1H, *J*= 12.8 Hz, H-6b), 4.00 (m, 1H, H-5), 2.09, 2.07, 2.03, 1.89 (4 s, 12H, 4 x –COCH$_3$), 1.59 (s, 9H), 1.53–1.44 (9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.5, 169.9, 169.3, 168.7 (4 x –COCH$_3$), 163.3, 155.9, 152.9, 144.6 (C4′), 120.9 (C5′), 85.5 (C-1), 83.2, 79.3, 75.0 (C-5), 72.7, 70.2, 67.6 (C-4), 61.5 (C-6), 36.2 (−CH$_2$NH–), 28.2, 28.0, 20.6, 20.5, 20.1 (4 x –COCH$_3$); ESI-MS: calcd for $C_{28}H_{43}N_6O_{13}$ ([M+H]$^+$): 671.2888, found: 671.2872.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-4-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidinomethyl-[1,2,3]-triazole (10b)

Yield=576 mg, 86 %; White fluffy powder; mp 75 °C; $[\alpha]_D^{25}$+3.9° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3418, 3339, 2979, 2934, 1756, 1642, 1620, 1567, 1458, 1419, 1371, 1319, 1227, 1135, 1058, 923; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.45 (s, 1H, –NHBoc), 8.70 (t, 1H, –CH$_2$NH–), 7.84 (s, 1H, H-5′), 5.83 (d, 1H, *J*=9.2 Hz, H-1), 5.61–5.51 (m, 2H, H-2 & H-4), 5.28–5.21 (m, 1H, H-3), 4.81–4.65 (m, 2H, –CH$_2$NH–), 4.26–4.10 (m, 3H, H-5, H-6a & H-6b), 2.22, 2.05, 2.01, 1.89 (4 s, 12H, 4 x –COCH$_3$), 1.53 (s, 9H), 1.48 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.3, 170.0, 169.8, 168.9 (4 x –COCH$_3$), 163.3, 156.0, 152.9, 144.5 (C4′), 121.0 (C5′), 86.1 (C-1), 83.2, 79.3, 74.0 (C-5), 70.8 (C-3), 67.8, 66.9, 61.3 (C-6), 36.3 (−CH$_2$NH–), 28.3, 28.0 (2C), 20.6, 20.5, 20.2 (4 x –COCH$_3$); ESI-MS: calcd for $C_{28}H_{43}N_6O_{13}$ ([M+H]$^+$): 671.2888, found: 671.2865.

1-(2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl)-4-*N*′,*N*″-bis(*tert*-butoxycarbonyl) guanidinomethyl-[1,2,3]-triazole (10c)

Yield=636 mg, 95 %; Yellow solid; mp 115–118 °C; $[\alpha]_D^{25}$ -15.2° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3332, 2979, 1749, 1638, 1560, 1374, 1324, 1236, 1138, 1049; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.46 (s, 1H, –NHBoc), 8.76 (t, 1H, –CH$_2$NH–), 7.83 (s, 1H, H-5′), 6.05 (d, 1H, *J*=10 Hz, H-1), 5.86 (d, 1H, *J*= 10.0 Hz, –NH2), 5.50 (t, 1H, *J*=9.6 Hz, H-3), 5.23 (t, 1H, *J*= 9.6 Hz, H-4), 4.73 (m, 2H, –CH$_2$NH–), 4.55–4.45 (m, 1H, H-2), 4.29 (dd, 1H, *J*=5.2 & 12.8 Hz, H-6a), 4.14 (dd, 1H, *J*=2.0 & 12.8 Hz, H-6b), 4.07–4.00 (m, 1H, H-5), 2.09, 2.07, 2.06 (3 s, 9H, 3 x –COCH$_3$), 1.78 (s, 3H, –NHCOCH$_3$), 1.52 (s, 9H), 1.48 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.9, 170.7, 169.5 (3 x –COCH$_3$ & –NHCOCH$_3$), 163.3, 156.0, 153.0, 144.3 (C4′), 121.9 (C5′), 85.6 (C-1), 83.3, 79.5, 74.8 (C-5), 72.2 (C-3), 68.2 (C-4), 61.8 (C-6), 53.2 (C-2), 36.3 (−CH$_2$NH–), 28.3, 28.1, 22.9 (−NHCOCH$_3$), 20.8, 20.7 (3 x –COCH$_3$); ESI-MS: calcd for $C_{28}H_{44}N_7O_{12}$ ([M+H]$^+$): 670.3048, found: 670.3034.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranosyl)-4-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidinomethyl-[1,2,3]-triazole (10d)

Yield=603 mg, 90 %; White fluffy powder; mp 91 °C; $[\alpha]_D^{25}$=−19.4° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3337, 3167, 2979, 2937, 1754, 1640, 1569, 1420, 1372, 1318, 1228, 1134, 1052, 914, 807, 770; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.44 (s, 1H, –NHBoc), 8.79 (t, 1H, –CH$_2$NH–), 7.80 (s, 1H, H-5′), 6.15 (d, 1H, *J*=0.8 Hz, H-1), 5.70 (m, 1H, H-2), 5.40–5.24 (m, 2H, H-3 & H-4), 4.78–4.64 (m, 2H, –CH$_2$NH–), 4.32 (dd, 1H, *J*=6.0 & 12.4 Hz, H-6a), 4.20 (dd, 1H, *J*=2.0 & 12.4 Hz, H-6b), 3.98 (m, 1H, H-5), 2.11, 2.10, 1.99 (3 s, 12H, 4 x –COCH$_3$), 1.51 (s, 9H), 1.48 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.6, 169.9, 169.7, 169.2 (4 x –COCH$_3$), 163.4, 156.1, 153.0, 144.3 (C4′), 121.4 (C5′), 84.8 (C-1), 83.4, 79.5, 75.6 (C-5), 70.8 (C-3), 68.9 (C-2), 65.0 (C-4), 62.3 (C-6), 36.3

(−$\underline{C}H_2NH$–), 28.3, 28.0, 20.8, 20.7, 20.6, 20.5 (4 x –$\underline{C}OCH_3$); ESI-MS: calcd for $C_{28}H_{43}N_6O_{13}$ ($[M+H]^+$): 671.2888, found: 671.2867.

1-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)-4-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidinomethyl-[1,2,3]-triazole (10e)

Yield=419 mg, 70 %; White solid; mp 116 °C; $[\alpha]_D^{25}$ -34.3° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 2979, 2936, 1756, 1641, 1619, 1567, 1453, 1417, 1370, 1324, 1293, 1227, 1157, 1135, 1085, 1059, 1044; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.42 (s, 1H, –N$\underline{H}$Boc), 8.76 (t, 1H, –$CH_2N\underline{H}$–), 7.78 (s, 1H, H-5′), 5.76 (d, 1H, *J*=8.0 Hz, H-1), 5.47–5.31 (m, 2H, H-2 & H-3), 5.16 (m, 1H, H-4), 4.71 (m, 2H, –$C\underline{H}_2NH$–), 4.31 (dd, 1H, *J*=5.6 & 11.6 Hz, H-5a), 3.61 (t, 1H, *J*= 11.6 Hz, H-5b), 2.08, 2.06, 1.89 (3 s, 9H, 3 x –$COC\underline{H}_3$), 1.52 (s, 9H), 1.48 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.0, 169.8, 168.9, (3 x –$\underline{C}OCH_3$), 163.3, 156.0, 153.0, 144.7 (C4′), 121.0 (C5′), 86.3 (C-1), 83.3, 79.5, 72.1, 70.4, 68.4 (C-4), 65.5 (C-5), 36.4 (−$\underline{C}H_2NH$–), 28.3, 28.1, 20.7, 20.6, 20.2 (3 x –$COCH_3$); ESI-MS: calcd for $C_{25}H_{39}N_6O_{11}$ ($[M+H]^+$): 599.2677, found: 599.2694.

1-[4-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl]-4-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidinomethyl-[1,2,3]-triazole (10f)

Yield=929 mg, 97 %; Fluffy powder; mp 115 °C; $[\alpha]_D^{25}$ -4.2° (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3449, 3341, 2979, 2937, 1754, 1641, 1621, 1568, 1420, 1371, 1321, 1229, 1135, 1057, 917; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.44 (s, 1H,–N$\underline{H}$Boc), 8.77 (t, 1H, –$CH_2N\underline{H}$–), 7.70 (s, 1H, H-5″), 5.81 (d, 1H, *J*=8.8 Hz, H-1), 5.46–5.34 (m, 3H, H-2, H-3 & H-4′), 5.18–5.10 (m, 1H, H-2′), 5.00–4.94 (m, 1H, H-3′), 4.78–4.66 (m, 2H, –$C\underline{H}_2NH$–), 4.55–4.44 (m, 2H, H-1′ & H-6a), 4.19–4.05 (m, 3H), 4.01–3.97 (m, 3H), 2.17, 2.11, 2.08, 2.07, 1.98, 1.87 (6 s, 21H, 7 x –$COC\underline{H}_3$), 1.52 (s, 9H), 1.48 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.4, 170.3, 170.2, 170.1, 169.6, 169.1 (2C) (7 x –$\underline{C}OCH_3$), 163.3, 156.0, 153.0, 144.5 (C4″), 121.0 (C5″), 101.1 (C-1′), 85.4 (C-1), 83.3, 79.5, 75.9, 75.6, 72.7, 70.9, 70.8, 70.4, 69.0, 66.6, 61.8, 60.9, 36.3 (−$\underline{C}H_2NH$–), 28.3, 28.1, 28.0, 20.8, 20.7 (3C), 20.5, 20.2 (7 x –$COC\underline{H}_3$); ESI-MS: calcd for $C_{40}H_{59}N_6O_{21}$ ($[M+H]^+$): 959.3733, found: 959.3730.

Synthesis of 5-[*N*′,*N*″-bis(*tert*-butoxycarbonyl)-S-methyl-isothioureido]-*N*′-[2(*S*)-2-benzyloxycarbonylamino]valeric acid benzyl ester (11)

S-Methyl-bis-Boc-isothiourea (264 mg, 1 mmol) was dissolved in dry DMF (5 mL). The mixture was cooled to 0 °C and sodium hydride (44 mg, 1.2 mmol) was added to this and the reaction mixture was allowed to stir at this temperature for 1 h. After 1 h, 2(*S*)-2-(benzyloxycarbonyl-amino)-5-iodovaleric acid benzyl ester (467 mg, 1.1 mmol) was added to this solution and the reaction mixture was allowed to stir at RT. After completion of the reaction as shown by TLC, DMF was removed in vacuo. Water (20 mL) was added and the mixture was extracted with ethyl actetate (3 x 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated to give the crude product which was subjected to column chromatography over silica gel (100–200 mesh) by using a mixture of ethyl acetate and hexane (10 %) to afford the pure product (**12**) as a colorless syrup (350 mg, 61 %). $[\alpha]_D^{25}$ +10.9° (c 1, $CHCl_3$); IR (Thin film, cm^{-1}): 3357, 2976, 2927, 2859, 1722, 1619, 1521, 1454, 1365, 1255, 1147, 1063, 970, 852; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39–7.27 (m, 10H, Ph), 5.60 (d, 1H, *J*=8.0 Hz, –N$\underline{H}$), 5.17 (s, 2H, –$C\underline{H}_2$Ph), 5.10 (s, 2H, –$C\underline{H}_2$Ph), 4.44–3.44 (m, 1H, –NHC$\underline{H}$CH_2–), 3.54 (t, 2H, *J*= 6.0 Hz, –NC$\underline{H}_2CH_2$–), 2.34 (s, 3H, –S$\underline{C}H_3$), 1.74–1.58 (m, 4H, –CC$\underline{H}_2C\underline{H}_2$C–), 1.48 (s, 9H) , 1.44 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.2, 163.0, 157.9, 156.1, 151.7, 136.3, 135.3, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 82.5, 81.9, 67.2, 66.9, 53.8 (−NH$\underline{C}$HCH_2–), 48.1 (−N$\underline{C}H_2CH_2$–), 29.7, 29.4, 28.1, 28.0, 25.1, 15.5 (−S$\underline{C}H_3$); ESI-MS: calcd for $C_{32}H_{44}N_3O_8S$ ($[M+H]^+$): 630.2849, found: 630.2846.

Synthesis of *N*-glucosylarginine with an amido linker (12)

A solution of 5-[*N*′,*N*″-bis(*tert*-butoxycarbonyl)-S-methyl-isothioureido]-*N*′-[2(*S*)-2-benzyloxycarbonylamino]valeric acid benzyl ester (**11**) (220 mg, 0.35 mmol) and *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)aminoacetamide (**2a**) (301 mg, 0.7 mmol) in dry THF was refluxed for 2 days. After completion of the reaction, solvent was evaporated under reduced pressure. Column chromatography of the crude product over silica gel (100–200 mesh) using a mixture of ethyl acetate and hexane (46 %) afforded the pure product (**12**) as a colorless syrup (180 mg, 52 %). $[\alpha]_D^{25}$ -4.6° (c 1, $CHCl_3$); IR (Thin film, cm^{-1}): 3369, 2977, 2935, 1752, 1724, 1621, 1523, 1456, 1371, 1229, 1150, 1040; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.15 (br s, 1H, –N$\underline{H}$), 7.70 (br s, 1H, –N$\underline{H}$), 7.34 (s, 10H, 2 x Ph), 5.63 (br s, 1H), 5.40–4.85 (m, 8H), 4.45–3.50 (m, 8H), 2.04, 2.03, 1.98 (3 s, 12H, 4 x –$COC\underline{H}_3$), 1.90–1.20 (m, 22 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.4, 172.0, 171.0, 170.6, 170.0, 169.6, 156.3, 156.0, 153.9, 150.5, 136.2, 135.5, 135.2, 128.6, 128.5, 128.3, 128.2, 128.0, 82.8, 82.0, 78.1, 77.8, 77.4, 73.6, 73.0, 70.4, 68.1, 67.3, 67.0, 61.8, 54.1, 53.8, 52.4, 46.8, 29.7, 29.4, 28.1, 25.0, 24.7, 20.7, 20.6; ESI-MS: calcd for $C_{47}H_{64}N_5O_{18}$ ($[M+H]^+$): 986.4246, found: 986.4246.

Synthesis of *N*′-(*n*-octyl)-*N*′,*N*″-bis(*tert*-butoxycarbonyl)-S-methylisothiourea (13)

S-Methyl-bis-Boc-isothiourea (580 mg, 2 mmol) was dissolved in dry DMF (5 mL). The mixture was cooled to

0 °C and sodium hydride (96 mg, 2.4 mmol) was added to this and the reaction mixture was allowed to stir at this temperature for 1 h. After 1 h, octyl bromide (0.4 mL, 2.2 mmol) was added to this solution and the reaction mixture was allowed to stir at RT. The work-up and purification of the crude product was carried out as described for compound **11** to afford the pure product (**13**) as a colorless syrup (483 mg, 60 %). $[\alpha]_D^{25}$ -0.3° (c 1, $CHCl_3$); IR (Thin film, cm^{-1}): 3398, 2955, 2926, 2856, 1723, 1622, 1457, 1388, 1366, 1250, 1144, 1107, 970, 855, 768; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.52–3.43 (m, 2H, –NC$\underline{H}_2$C–), 2.38 (s, 3H,–SC$\underline{H}_3$), 1.70–1.58 (m, 2H), 1.51 (s, 9H), 1.48 (s, 9H), 1.33–1.18 (m, 10H, 5 x–C$\underline{H}_2$–), 0.87 (t, 3H, –C$\underline{H}_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 163.2, 158.0, 151.9, 82.1, 81.8, 49.1 (−N$\underline{C}H_2$–), 31.8, 29.3, 29.2, 28.9, 28.2, 28.1, 28.0, 26.8, 22.7, 15.6 (−S$\underline{C}H_3$), 14.1 (−$CH_2\underline{C}H_3$); ESI-MS: calcd for $C_{20}H_{39}N_2O_4S$ ($[M+H]^+$): 403.2631, found: 403.2630.

Synthesis of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(*n*-octyl)-*N*′,*N*″-bis(*tert*-butoxycarbonyl) guanidinoacetamide (14)

A solution of *N*′-(*n*-octyl)-*N*′,*N*″-bis(*tert*-butoxycarbonyl)-S-methylisothiourea (**13**) (300 mg, 0.75 mmol) and *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)aminoacetamide (**2a**) (643 mg, 1.5 mmol) in dry THF was refluxed for 2 days. After completion of the reaction, crude product was purified by column chromatography over silica gel (100–200 mesh) using a mixture of ethyl acetate and hexane (32 %) to afford the pure product (**14**) as a colorless syrup (230 mg, 41 %). $[\alpha]_D^{25}$ -6.7° (c 1, $CHCl_3$); IR (Thin film, cm^{-1}): 3342, 2956, 2929, 2858, 1754, 1714, 1673, 1660, 1623, 1516, 1455, 1370, 1232, 1150, 1042, 981, 908, 762; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H,–CH_2N$\underline{H}$–), 7.81 (d, 1H, *J*=8.0 Hz, –N$\underline{H}$1), 5.35–5.21 (m, 2H, H-1 & H-3), 5.07 (t, 1H, *J*=9.6 Hz, H-4), 4.97 (t, 1H, H-2), 4.30 (dd, 1H, *J*=3.6 and 10.0 Hz, H6a), 4.17–3.47 (m, 6H, H-5, H6b, –C$\underline{H}_2$NH– & –NC$\underline{H}_2CH_2$–), 2.08, 2.04, 2.02 (3 s, 12H, 4 x –COC$\underline{H}_3$), 1.70–1.58 (m, 2H, –$NCH_2C\underline{H}_2$–), 1.59–1.40 (m, 18H), 1.40–1.12 (m, 12H), 0.88 (t, 3H,–$CH_2C\underline{H}_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.4, 170.3, 169.9, 169.7, 169.4, 153.9, 150.4, 143.8, 82.5, 81.8, 78.2 (C-1), 73.6 (C-5), 72.9 (C-3), 70.4 (C-2), 68.2 (C-4), 61.8 (C-6), 52.4 (−$\underline{C}H_2$NH–), 47.7 (−N$\underline{C}H_2CH_2$–), 46.4, 31.7, 31.6, 29.7, 29.3, 29.1, 28.9, 28.1, 26.8, 24.7, 22.6, 20.7, 20.6 (2C), 14.1; ESI-MS: calcd for $C_{35}H_{59}N_4O_{14}$ ($[M+H]^+$): 759.4028, found: 759.4017.

Synthesis of *N*-(β-D-glucopyranosyl)-*N*′-(*n*-octyl)guanidinoacetamide.hydrochloride (15)

Fully protected glucosylguanidinoacetamido lipid (**14**) (0.3 mmol) was deprotected using the same procedure as described for compounds **4a**-**4c** to afford a white precipitate of hydrochloride salt of *N*-(β-D-glucopyranosyl)-*N*′-(*n*-octyl)guanidinoacetamide (**15**) (107 mg, 83 %) yield. $[\alpha]_D^{25}$ -108.4° (c 1, H_2O); IR (Thin film, cm^{-1}): 3685, 3659, 3641, 3628, 3622, 3610, 3598, 3578, 3558, 3331, 2926, 2861, 2370, 2336, 1658, 1649, 1638, 1589, 1570, 1552, 1544, 1456, 1449, 1430, 1413, 1260, 1075, 1040; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.98 (d, 1H, *J*=8.8 Hz, H-1), 4.05 & 4.00 (ABq, 2H, –C$\underline{H}_2$NH–), 3.83 (dd, 1H, *J*= 5.2 Hz & 12.6 Hz, H-6a), 3.67 (dd, 1H, *J*=5.2 & 12.6 Hz, H-6b), 3.54–3.29 (m, 4H, H-2, H-3, H-4 & H-5), 3.17 (t, 2H, –NC$\underline{H}_2CH_2$–), 1.52 (m, 2H,–$NCH_2C\underline{H}_2$–), 1.32–1.14 (m, 10H, 5 x –CH_2–), 0.79 (t, 3H, –$CH_2C\underline{H}_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.0 (−NH$\underline{C}OCH_2$–), 156.2, 79.2 (C-1), 77.5, 76.3, 71.6, 69.0, 60.4 (C-6), 43.6 (−$\underline{C}H_2$NH–), 41.5 (−NC$\underline{H}_2CH_2$–), 31.2, 28.5, 27.9, 26.0, 22.1, 13.5 (−$\underline{C}H_3$); ESI-MS: calcd for $C_{17}H_{35}N_4O_6$ ($[M+H]^+$): 391.2557, found: 391.2565.

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