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Sugar-based peptidomimetics as potential inhibitors of the vascular endothelium growth factor binding to neuropilin-1

Alexandre Novoa [a], Nadia Pellegrini-Moïse [a], Denise Bechet [b], Muriel Barberi-Heyob [b], Yves Chapleur [a,*]

[a] Groupe SUCRES, UMR 7565, Nancy Université-CNRS, BP 70239, F-54506 Vandœuvre-lès-Nancy, France
[b] CRAN, UMR 7039, Nancy Université-CNRS, Centre Alexis Vautrin, Avenue de Bourgogne, F-54511 Vandœuvre-lès-Nancy, France

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ABSTRACT

Neuropilin-1 (NRP-1) is a co-receptor of $VEGFR_{165}$ and molecules interfering with $VEGF_{165}$ binding to NRP-1 seem to be promising candidates as new angiogenesis modulators. Based on the minimal four amino acid sequence of peptidic ligands known to bind NRP-1, we describe here the design, synthesis and biological evaluation of series of original sugar-based peptidomimetics using a *C*-glycosyl compound, derived from D-gulonolactone, as a scaffold, which was functionalized with side chains of the amino-acids arginine, and tryptophane or threonine. At 100 μM, all compounds exhibited a weak affinity for NRP-1, the most efficient being the bis-guanidinylated compound **32** (IC_{50} = 92 μM) which could be considered as a new NRP-1 non-peptidic ligand.

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1. Introduction

Angiogenesis or formation of new blood vessels is an important biological process under healthy physiological conditions and in variety of diseases including cancer.[1] Vascular endothelial growth factors (VEGFs) are key molecules in blood vessel formation and represent the most important growth factors involved in tumor angiogenesis.[2] Among growth factors over-expressed during angiogenesis, $VEGF_{121}$ and $VEGF_{165}$ are major isoforms, mediating their biological effects through receptors located on the endothelial cells, that is, VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR). Neuropilin-1 (NRP-1), identified as a co-receptor of $VEGF_{165}$, the most abundant isoform is a 140 kDa membrane protein, with a large extracellular domain and a short cytoplasmic tail. NRP-1 was first identified as a receptor for semaphorin, a family of axonal chemorepellent proteins. In the nervous system, this receptor forms a high affinity semaphorin-binding complex with a receptor tyrosine kinase, plexin that mediates semaphorin-induced growth cone collapse. On the endothelium, NRP-1 is expressed together with VEGFR-2. Therefore, NRP-1 directly binds $VEGF_{165}$ and acts as a co-receptor along with VEGR-2.[3] It was also reported that NRP-1 forms a ternary complex between $VEGF_{165}$, VEGFR-2 and NRP-1.[4] NRP-1 potentiates KDR-mediated endothelial cells migration and proliferation. Moreover, some tumor cells can express high levels of NRP-1, which is typically their only $VEGF_{165}$ receptor. Indeed, the latter mediates effects on tumor progression and tumor angiogenesis.[5] For these reasons, molecules that interfere with $VEGF_{165}$ binding to NRP-1 can modulate the behavior of cancer and endothelial cells. NRP-1 seems to be a promising target in the development of new angiogenic modulators and in targeting strategies. Peptide inhibitors of NRP-1 currently in development for use as antiangiogenic agents, are all basic in character and function and incorporate an arginine residue.[6] Recently, several peptides have been reported to modulate VEGF-NRP-1 binding and studies have revealed structural basis for ligand binding to NRP-1. A bicyclic peptide antagonist (EG 3287) has been characterized and showed the importance of the *C*-terminal six amino-acid domain encoded by exon 8 for NRP-1 binding which corresponds to the CDKPRR sequence.[7] These conclusions were further confirmed by the discovery that the tuftsin peptide (TKPR) selectively binds to NRP-1 and blocks VEGF binding to that receptor.[8] The crystal structure of NRP-1 in complex with tuftsin provided the first structural information of NRP-1 in interaction with a ligand. The *C*-terminal arginine of tuftsin mainly contributes to the interaction between tuftsin and NRP-1.[9] A cyclic peptide (CPQPRPLC sequence) isolated from a random phage display library has been validated as a VEGF-R ligand targeting NRP-1. NMR spectroscopy has shown that receptor binding is mediated by the RPL pattern.[10,11] Interestingly, a heptapeptide ATWLPPR, selected by screening a phage display library, was described as an effective antagonist of VEGF binding to NRP-1 and can be considered as a potent inhibitor of tumor angiogenesis (IC_{50} = 19 μM).[12] Structure-function analyses of ATWLPPR based on alanine-scanning or amino acid deletion showed the importance of the *C*-terminal sequence LPPR and particularly the key role of *C*-terminal arginine.[13] Moreover, ATWLPPR

* Corresponding author. Tel.: +33 3 83 68 47 73; fax: +33 3 83 68 47 80.
E-mail address: yves.chapleur@srsmc.uhp-nancy.fr (Y. Chapleur).

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has recently been conjugated to a TriPhenylChlorin type (TPC) photosensitizer via a 6-aminohexanoic acid (Ahx) spacer. The coupling compound TPC-Ahx-ATWLPPR binds to NRP-1 (IC_{50} = 171 μM), targeting endothelial cells and tumor cells, and exhibits enhanced efficiency in in vitro photodynamic therapy (PDT) as compared to TPC alone.[14] TPC-Ahx-ATWLPPR was stable in vitro in human and mouse plasma for at least 24 h but following intra-venous injection in glioma-bearing nude mice, was degraded in vivo at various rates, depending on the organ considered. TPC-Ahx-A was identified as the main metabolic product, and biodistribution studies suggested that its appearance in plasma mainly resulted from the degradation of the peptidic moiety into organs of the reticuloendothelial system. According to in vitro cell culture experiments, TPC-Ahx-ATWLPPR was significantly degraded after incorporation in human umbilical vein endothelial cells, mainly into TPC-Ahx-A.[15]

Given the poor bioavailability and instability of peptidic ligands, the design of small molecules as peptidomimetics, targeting endothelial cells is attractive.[16] The use of carbohydrates as scaffolds to construct new active compounds for mimicking bioactive peptides has emerged in the last 10 years. The first example of the use of a monosaccharide as template for the construction of peptidomimetics was related to somatostatin.[17] Since these works, the use of carbohydrates as scaffolds for the construction of bioactive compounds has been reported.[18]

In connection with our ongoing program on the design of sugar-based peptidomimetics[18c,m,n] we describe here the design, synthesis and biological evaluation of series of sugar-based peptidomimetics inspired by known NRP-1 peptidic ligands, that is, ATWLPPR. The choice of the carbohydrate scaffold was done by visual analogy with the heptapeptide. The LPP sequence was considered as a rigid scaffold bearing arginine and tryptophane or threonine. Thus, we proposed the use of a lipophilic and rigid sugar template to replace the LPP scaffold. The trioxabicyclo[3.3.0] system readily accessible from sugar γ-lactones was envisioned as a good starting point and was decorated with mandatory guanidine/arginine residue, present on both peptides. The two other significant residues tryptophane and threonine should be mimicked by an appropriate side chain (Fig. 1).

2. Chemistry

On the basis of our experience and literature precedents, we planned to construct a *C*-glycosyl-sugar amino acid suitable for further functionalization at both ends. Our synthetic plan implied on the one hand the introduction of tryptophane and threonine side chains by amide bond formation. On the other hand, introduction of a guanidine function or a mimetic group thereof, should be performed by reductive amination of a suitable aldehyde easily obtained by diol cleavage.

Our first target was the carboxylic acid **3** (Scheme 1). The known *exo*-glycal **1** was prepared from the corresponding protected D-gulonolactone by a Wittig reaction and obtained as a mixture of stereoisomers (*E*/*Z* 1.2:1) in 80% yield.[19] The two isomers were easily separated by chromatography. Starting from the *E*-isomer, the saturated ester **2** was obtained in excellent yield (98%) by reductive hydrogenation in ethyl acetate in presence of 10 mol % of Pd/C. Interestingly, hydrogenation of *Z*-isomer proceeded via prior isomerization to *E*-isomer and thus needed 40 mol % of Pd/C to provide the saturated compound **2** in 60% yield. Hydrogenation of *exo*-glycal **1** proceeds via a high stereocontrol of double bond reduction from the less crowded β face and led to compound **2** with the methoxycarbonylmethyl moiety on the α face as indicated by the $J_{3,4}$ = 4 Hz (ulosonic acid numbering) coupling constant in favor of a cis arrangement of H-3 and H-4 protons.[20] Saponification of **2** in a THF/H_2O mixture in presence of KOH led to the key acid **3** in 98% yield. Using carbonyldiimidazole as activating agent, amides **4** and **5** were obtained in 86% and 78% yield by coupling **3** with tryptamine and 1-(*R*)-aminopropan-2-ol as mimetic groups of tryptophane and threonine side chain, respectively. In view of further chemical manipulations, protection of the hydroxyl function of amide **5** was achieved in quantitative yield by treatment with acetic anhydride in pyridine. Selective removal of the exocyclic isopropylidene acetal on compounds **4** and **6** under several acidic conditions has been investigated. The use of acetic acid in a mixture of THF/H_2O at 65 °C and PPTS (15 mol %) in MeOH furnished the mono deprotected compound in modest yields (40% and 30%, respectively). The most efficient method was the use of aqueous HCl in MeOH (1:3) which furnished diols **7** and **8** in 93% and 78%, respectively. Oxidative cleavage of the diol moiety by $NaIO_4$ gave aldehydes **9** and **10** in good yields (92% and 78%, respectively). These aldehydes have been isolated as partial hydrates without detectable epimerisation as confirmed by the structure of the amines **11**–**22** prepared by reductive amination.

As known from the literature, in the RGD sequence mimics, the guanidine function of the R residue may be replaced by guanidine or amidine surrogates.[21] Starting from the functionalized aldehydes **9** and **10**, different amines commonly used as guanidine mimetics were introduced by reductive amination.[22] To this end, various nucleophiles commercially available or prepared by routine chemistry from readily available starting materials were used (Table 1).[23] Reductive aminations have been carried out in MeOH in the presence of acetic acid and $NaBH_3CN$. The expected amines **11**–**22** were prepared in modest to good yields as pure isolated compounds (Scheme 2, Table 1). Compounds **18** and **21** were difficult to purify and thus isolated in rather low yields. The acetyl function of compounds **18**–**21** was removed using Zemplen method giving compounds **23**–**27** in excellent yields (Table 1).

For the introduction of a guanidine group, the *C*-glycosyl compounds **17** and **22** bearing a diaminoethane spacer were prepared. Removal of the Cbz protecting group of compounds **17** and **22** was achieved by catalytic hydrogenation giving compounds **28** and **29** in good yield (Scheme 3). Treatment of the free amines **28** and **29** with *N*,*N*′-bis(benzyloxycarbonyl)-*S*-methylisothiourea in excess in DMF in the presence of $HgCl_2$ gave guanidinylated derivatives.[24] However, careful examination of ^1H and ^{13}C NMR showed that the isolated compounds were the bis-guanidinylated deriva-

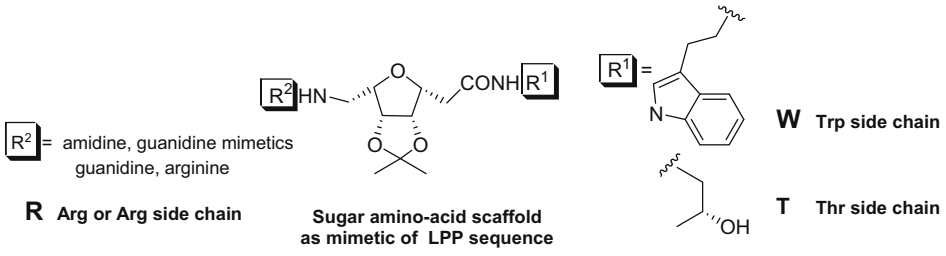
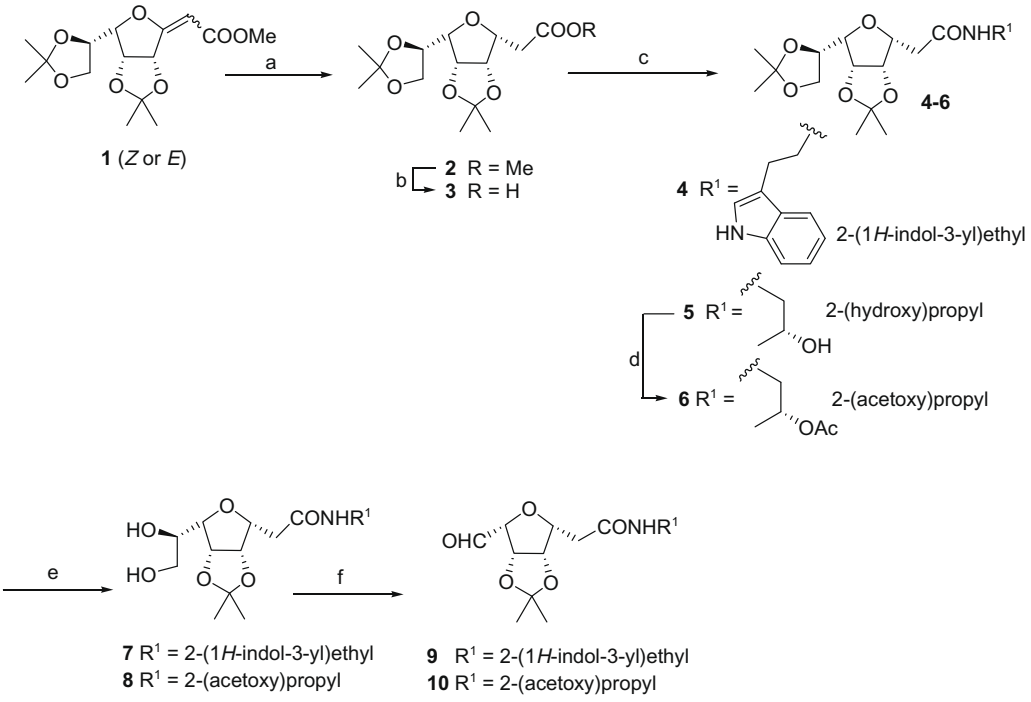


Figure 1. Design of sugar-based peptidomimetics.



Scheme 1. Reagents and conditions: (a) H_2, Pd/C, EtOAc, 25 °C, 24 h, [98% for *E*-isomer; 60% for *Z*-isomer]; (b) KOH, THF/H_2O (1:1), 25 °C, 24 h, 98%; (c) R^1NH_2, CDI, THF, 25 °C, 12 h, [86% for **4**; 78% for **5**]; (d) Ac_2O, pyridine, 25 °C, 12 h, 99%; (e) HCl (1 N)/MeOH (1:3), 0–25 °C, [12 h, 93% for **7**; 6 h, 78% for **8**]; (f) $NaIO_4$, MeOH, 25 °C, 14 h, [92% for **9**; 78% for **10**].

tives **30** or **31** resulting from the reaction of both primary and secondary amine groups of **28** and **29**. Removal of Cbz protecting group of **30** by catalytic hydrogenation yielded the expected guanidinoglycoside **32**. On hydrogenation of compound **31** in MeOH, concomitant removal of the acetyl group occurred giving the fully deprotected compound **33**. The presence of two guanidine functions was unambiguously confirmed by mass spectrometry and ^{13}C NMR spectra, two signals, characteristic of guanidine groups, being observed around δ 150 ppm.

To overcome this difficulty, the introduction of the guanidine function under Mitsunobu conditions was explored (Scheme 4).[25] Starting from the aldehyde **9**, alcohol **34** was obtained in 45% yield by reductive amination with 3-aminopropanol. Activation of the primary alcohol with triphenylphosphine and diethylazodicarboxylate followed by treatment with *N*,*N*′,*N*‴-tri-(*tert*-butoxycarbonyl)guanidine gave compound **35**. This compound results from intramolecular nucleophilic attack of the secondary amine on the *tert*-butoxycarbonyl protecting group of the guanidine residue leading to a five membered ring as confirmed by mass spectrometry. Removal of the two remaining *tert*-butoxycarbonyl protecting groups was achieved by acidic treatment (TFA) giving the cyclic urea **36** in 72% yield.

To solve the problem raised by the presence of the secondary amine on compounds **17** and **22**, introduction of the guanidine function was planned using the previously used efficient reductive amination of aldehydes **9** and **10**. In this case the *N*-(2-aminoethyl)-*N*′,*N*‴-bis-(*tert*-butoxycarbonyl)guanidine prepared according to literature procedures was used as the amine component (Scheme 5).[23b] This way, the protected guanidinoglycosides **37** and **38** were obtained in about 40% isolated yield. The removal of *tert*-butyloxycarbonyl groups was achieved by acidic treatment with TFA in CH_2Cl_2.

Taking into account the position, at the *C*-terminus, of the arginine residue in all peptidic ligands of NRP-1 it was reasoned that its carboxylic function may play a role in the recognition process. Thus, we attempted to introduce a whole arginine residue on our scaffold. Based on some literature precedents, N-alkylation of L-arginine amino acid by reductive amination seemed reasonable.[26] For easier chemical manipulation, the reaction was carried out with L-arginine methyl ester hydrochloride on both aldehydes **9** and **10** (Scheme 6). Amines **41** and **42** were obtained in 75% and 68% yield, respectively, after purification on reverse phase column chromatography. Hydrolysis of the methyl ester was performed by treatment with LiOH in a THF/water mixture (3:1). The resulting peptidomimetic compounds **43** and **44** have also been purified by reverse phase chromatography and obtained in good yields (68% and 87%, respectively).

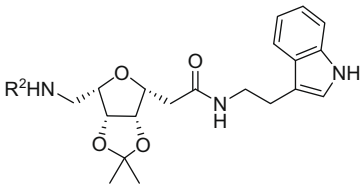
3. Biological evaluation

The binding of peptidomimetic derivatives to recombinant NRP-1 protein was determined using a competition assay previously described by Tirand et al.[14] Briefly, biotinylated $VEGF_{165}$ was incubated with recombinant chimeric NRP-1 protein in the presence of the compound to be tested. The biotinylated $VEGF_{165}$ remaining after washing steps was detected by chemiluminescence thanks to HRP-conjugated streptavidin. The binding of biotinylated VEGF (negative control) to recombinant chimeric NRP-1 protein was evaluated in the presence of $VEGF_{165}$ and ATWLPPR as positive controls. Affinities were estimated as IC_{50} values, that is, the concentration of competitor that displaced 50% of biotinylated $VEGF_{165}$ binding, using the medium effect method.

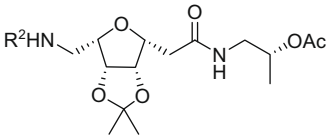
A preliminary screening with inhibitor concentrations of 100 μM was performed. At this concentration, all the compounds exhibited a modest affinity for NRP-1 as compared to the affinity of the reference peptide ATWLPPR (Figs. 2–4).

In the tryptamine series, mimicking tryptophane side chain, the use of aromatic or heteroaromatic guanidine surrogates as in compounds **11–16** seems deleterious to the activity as compared to a guanidinyl group which induces the activity of compounds **36**–**37** and **39**. It seems important for the guanidyl group to be on a flexible

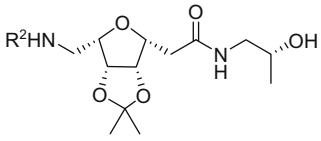
Table 1
Reductive amination of aldehydes **9** and **10**



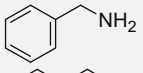
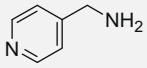
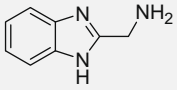
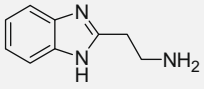
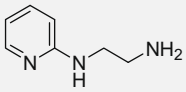
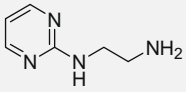
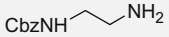
11-17

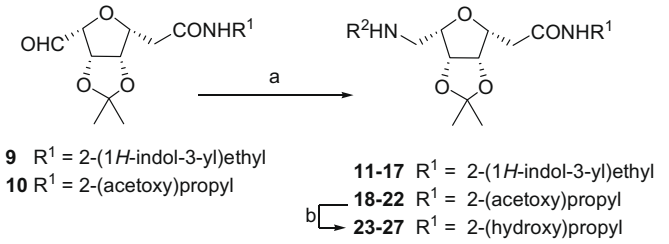


18-22



23-27

Entry	R^2NH_2	2-(1*H*-Indol-3-yl)ethyl series		2-(Acetoxy)propyl series		2-(Hydroxy)propyl series	
		Product	Yield (%)	Product	Yield (%)	Product	Yield (%)
1		**11**	55	–	–	**23**	40 (two steps)
2		**12**	55	**18**	25	**24**	70
3		**13**	50	**19**	45	**25**	85
4		**14**	55	**20**	50	**26**	80
5		**15**	47	**21**	25	**27**	82
6		**16**	45	–	–	–	–
7		**17**	50	**22**	75	–	–



Scheme 2. Reagents and conditions: (a) R^2NH_2, $NaBH_3CN$, MeOH/AcOH (15:1), 0–25 °C, 24 h; (b) Na°, MeOH, 25 °C, 20 min.

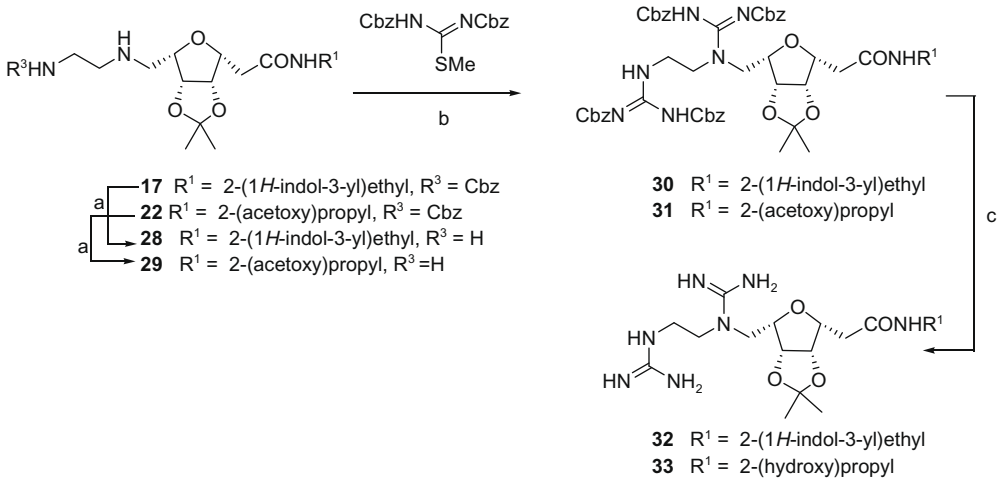
arm like in the acyclic analogs **37** and **39** as deduced from the weaker activity of compounds **35** and **36** in which the guanidyl group is embedded in a cycle. Moreover, significant improvement of activity is observed with guanidinyl residues as in compounds **30** and **32**. These results confirm that a guanidyl group is a primary requirement for a significant activity and that surrogates of this group, often used for example to mimic the RGD sequence,[21] are not useful here. In this series, the most potent compound is the fully deprotected glycoside **32** which exhibited 65% inhibition for NRP-1 at 100 μM and for which an IC_{50} = 92 μM was determined (Fig. 2).

Concerning the two other series, the compounds have been tested with and without the hydroxyl protection, as a way to explore the significance of the OH group on the binding (Figs. 3 and 4). As depicted on Figs. 3 and 4, the peptidomimetics containing a hydroxyl group are slightly more potent than the corresponding acetylated compounds, suggesting that the hydroxyl group of the threonine mimic does not play an essential role in the binding of our compounds on NRP-1. In these series, the presence of a guanidine function in compounds **31, 33**, **38** and **40** failed to displace the binding of biotinylated $VEGF_{165}$ to NRP-1, compared to guanidine surrogates for compounds **18–21** and **23–27**.

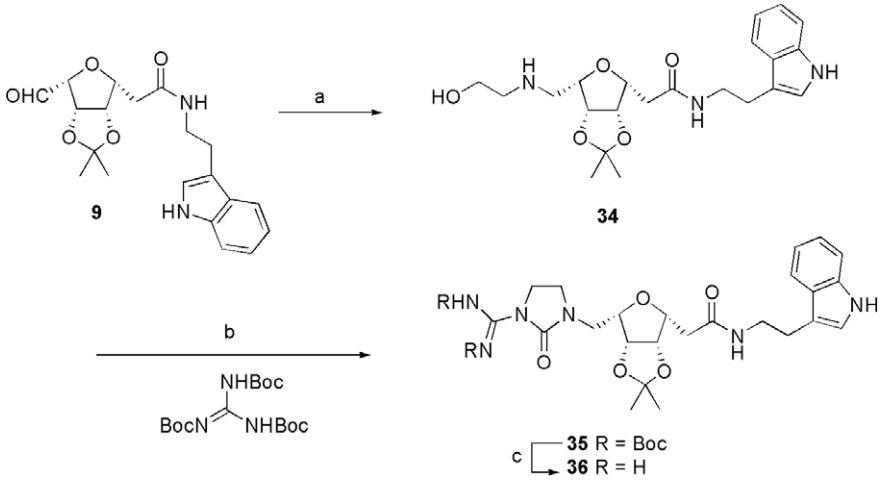
The reported studies showing the key role of *C*-terminal arginine in ATWLPPR led to the hypothesis of a possible role of the carboxylic function of the R residue when located at the *C* terminus as in the model compound ATWLPPR.[13] However, the modest activity of compounds **43** and **44** bearing a *N*-linked arginine residue, is somewhat disappointing and suggests that other important factors are involved in the binding to NRP-1.

The binding to NRP-1 of the most affine compound **32** was determined in the range of concentrations varying from 10 μM to 500 μM. Indeed, the compound **32** showed affinity for NRP-1 (IC_{50} = 92 μM, Fig. 5). However, we previously evaluated VEGF plasma levels in nude mice xenografted with U87 cells; plasma concentrations of VEGF (165 and 121 isoforms) were around 25 pg/mL (0.5–0.7 pM) lower than K_d values (K_d ~10–700 pM), considering a molecular weight of 35 and 45 kDa for $VEGF_{121}$ and $VEGF_{165}$ homodimers, respectively.[15c] Hence, it is also interesting to note that the level of $VEGF_{165}$ in the blood compartment can not hinder the recognition of the peptidomimetic **32** by NRP-1. A non-specific binding due to the highly basic character of this compound, should be excluded taking into account the weaker affinity of bis-guanidine compound **33**.

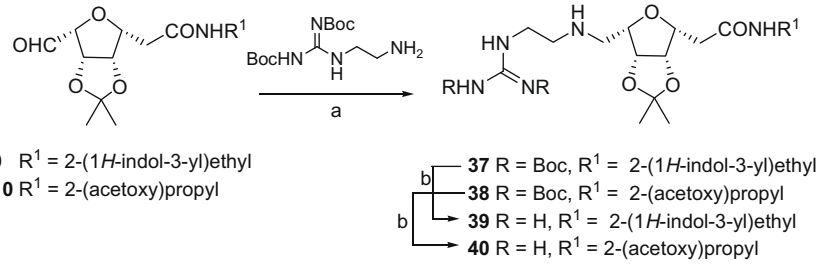
To sum up this study, it appears that a tryptophane mimic and a genuine guanidine residue are required to obtain some activity, the most potent compound **32** fulfill these requirements and exhibits an IC_{50} of 92 μM. Mimics of threonine even with guanidine residue led to less active compounds. The incorporation of a terminal arginine residue in compounds **43** and **44** did not improve significantly the inhibition in contrast with a recent report.[27]



Scheme 3. Reagents and conditions: (a) H_2, Pd/C, MeOH, 25 °C, 24 h, [90% for **28**, 98% for **29**]; (b) $HgCl_2$, DMF, NEt_3, 25 °C, 14 h, [35% for **30**, 25% for **31**]; (c) H_2, Pd/C, MeOH, 25 °C, 24 h, [90% for **32** and **33**].



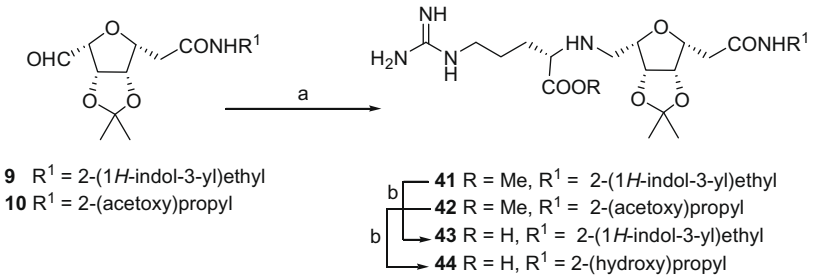
Scheme 4. Reagents and conditions: (a) (i) HO–$(CH_2)_2$–NH_2, Et_3N, Ti(O*i*Pr)$_4$, MeOH, MS 4 Å, 25 °C, 20 h; (ii) $NaBH_4$, 0 °C, 2 h, 45%; (b) DEAD, PPh_3, THF, 25 °C, 18 h, 35%; (c) TFA, CH_2Cl_2, 0–25 °C, 72%.



Scheme 5. Reagents and conditions: (a) $NaBH_3CN$, MeOH (15:1), AcOH, 25 °C, 24 h, [40% for **37** and **38**]; (b) TFA, CH_2Cl_2, 0–25 °C [80% for **39**; 38% for **40**].

4. Conclusion

In conclusion, in this pioneering study to design non-peptidic ligands of NRP-1, new peptidomimetics based on known peptidic ligands were prepared starting from a sugar bicyclic system as a rigid scaffold. The synthesized compounds showed a modest affinity for the recombinant chimeric NRP-1 protein. The most potent compound **32** exhibiting an IC_{50} of 92 μM. These results lead us to suggest that our scaffold does not efficiently replace the LPP sequence present in the heptapeptide ATWLPPR and must be tuned to arrange the crucial residues (guanidine and indole) in the appropriate spatial directions. These results may also suggest the need for another, yet to be discovered, interaction in the receptor with a residue not present in our compounds. Further work is in progress to improve the potency of this lead structure.



Scheme 6. Reagents and conditions: (a) L-ArgOMe.HCl, $NaBH_3CN$, MeOH/AcOH (15:1), 25 °C, 24 h, [75% for **41**; 68% for **42**]; (b) LiOH, H_2O/THF (1:3), 25 °C, 24 h, [68% for **43**; 87% for **44**].

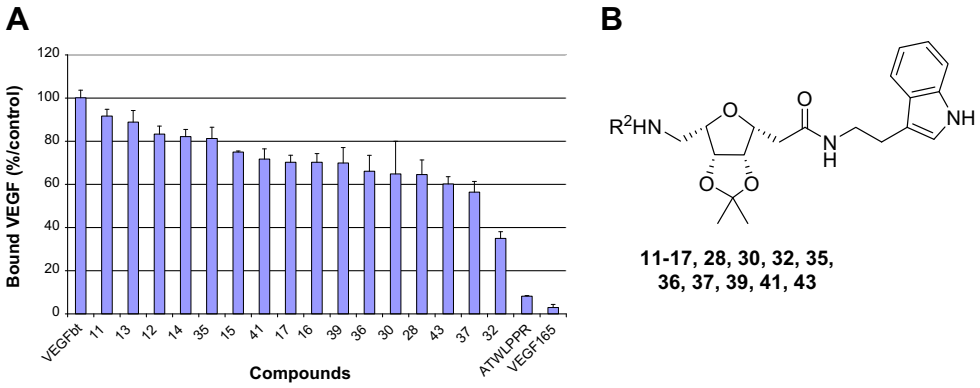


Figure 2. (A) Binding of biotinylated VEGF to NRP-1in the presence of $VEGF_{165}$, ATWLPPR and new synthesized compounds at 100 μM. Vertical bars represent S.D. for $n = 3$ experiments. (B) General structure of the [2-(1*H*-indol-3-yl)ethyl] series.

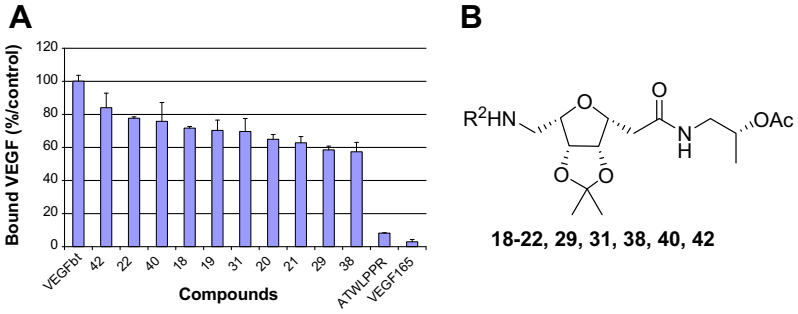


Figure 3. (A) Binding of biotinylated VEGF to NRP-1in the presence of $VEGF_{165}$, ATWLPPR and new synthesized compounds at 100 μM. Vertical bars represent S.D. for $n = 3$ experiments. (B) General structure of the [2-(acetoxy)propyl] series.

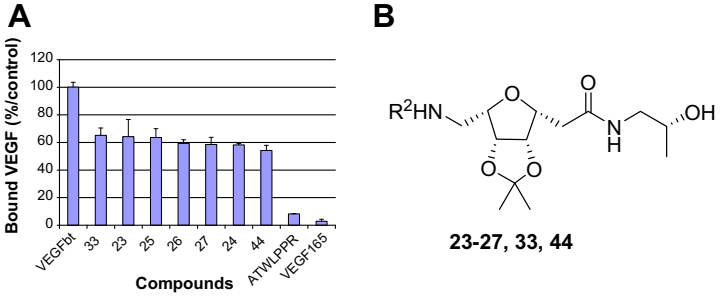


Figure 4. (A) Binding of biotinylated VEGF to NRP-1in the presence of $VEGF_{165}$, ATWLPPR and new synthesized compounds at 100 μM. Vertical bars represent S.D. for $n = 3$ experiments. (B) General structure of the [2-(hydroxy)propyl] series.

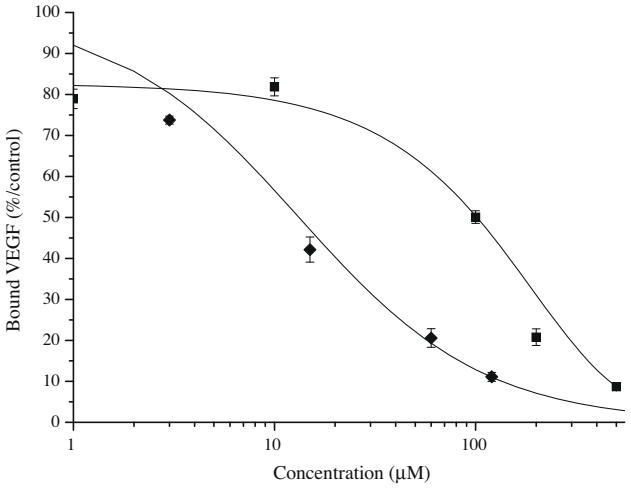


Figure 5. Binding of biotinylated VEGF (5 ng/mL; 110 pM) to recombinant NRP-1 protein in the presence of 2 μg/mL heparin was evaluated when increasing concentrations of ATWLPPR (lozenge) and compound **32** (square). Data points show the mean ± S.D.; $n = 3$.

5. Experimental part

5.1. General

Solvents and liquid reagents were purified and dried according to recommended procedures. All commercially available chemicals were obtained from Sigma–Aldrich. TLC analyses were performed using standard procedures on Kieselgel 60 F_{254} plates or RP-18 F_{254} plates (Merck). Compounds were visualized using UV light (254 nm) and (or) a solution of cerium sulfate tetrahydrate and phosphomolybdic acid in 10% aqueous sulfuric acid as developing agent. A specific revelator for guanidine function has been used in several cases: successive spraying of 0.1% of 2-naphthol in 4% NaOH aqueous and of 2% of Br_2 in 4% NaOH aqueous. Column chromatography was performed on Silica Gel SI 60 (63–200 μm) (Merck). Preparative reverse phase chromatography was performed on LiChroprep®RP-18 (40–63 μm) (Merck). FTIR spectra were recorded on a Perkin–Elmer spectrum 1000 on NaCl windows or KBr pellets. Melting points were determined with a Tottoli apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 141 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer AC250 (250 MHz and 62.9 MHz, respectively) and DRX400 (400 MHz and 100.6 MHz, respectively). For complete assignment of ^{1}H and ^{13}C signals, two-dimensional ^{1}H, ^{1}H COSY and ^{1}H, ^{13}C correlation spectra were recorded. Chemical shifts (δ) are given in ppm relative to the solvent residual peak. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broad signal. The *J* values given refer to apparent multiplicities and do not represent the true coupling constants. Mass spectra were obtained on a VG-Platform Micromass-Waters (ESI$^+$/quad) and a Shimadzu GCMS-QP2010 apparatus (CI). HRMS spectra were recorded on a Bruker MicroTOFq apparatus.

5.2. Binding of peptidomimetic derivatives to recombinant NRP-1 protein

Neuropilin-1 was obtained from R&D Systems (Lille, France), as recombinant chimeric protein. The surface of Maxisorp microplates (Dutscher) was coated with NRP-1 (2 μg/mL) in phosphate buffered saline (PBS), overnight at room temperature. The plates were blocked with phosphate buffer saline (PBS) containing 0.5% bovine serum albumin (BSA, blocking buffer) during 1 h at 37 °C, to prevent non-specific interactions. Binding of the peptidomimetic derivatives to NRP-1 was assessed using 5 ng/mL of biotinylated $VEGF_{165}$ (R&D Systems) in blocking buffer containing 2 μg/mL heparin. Biotinylated $VEGF_{165}$ was added to the coated wells, in competition with an excess of derivatives, alone without any addition (negative control) or unlabelled $VEGF_{165}$ as positive control of binding (0.5 μg/mL, R&D Systems). ATWLPPR (100 μM), 0.5% Tween-20 was also used as positive control. After a 2 h-incubation at room temperature, the plates were washed and the amount of bound biotinylated $VEGF_{165}$ stained with streptavidin horseradish peroxidase conjugate (R&D Systems) and assayed. After 20 min at room temperature, reaction was stopped by the addition of Stop Solution (R&D Systems). Optical densities were measured at 450 nm. Results were expressed as relative absorbance to wells containing only blocking buffer. Three wells per condition were used for each compound. The assay was performed according to Tirand et al. [14].

5.3. Methyl 3,6-Anhydro-2-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*gulo*-L-*glycero*-octonic acid methyl ester (2)

To a solution of **1** (100 mg, 0.32 mmol) in ethyl acetate (10 mL) was added Pd/C (10%) (10% w/w for **1*E***, 40% w/w for **1*Z***). The mixture was then stirred under H_2 atmosphere. After 24 h, the reaction mixture was filtered through a pad of Celite and the solvent removed in vacuo to give **2** as a white solid. The crude compound was used without further purification. Yield 99% from **1*E***, 60% from **1*Z*** as a white solid; $R_f = 0.42$ (hexane/EtOAc 1:1). Mp = 91–93 °C (recrystallized from hexane/CH_2Cl_2); $[\alpha]_D^{20} = -11$ (*c* 0.4, $CHCl_3$); IR (film) *v* 2980, 2930, 2873, 1787, 1742 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.29 (s, 3H), 1.39 (s, 3H), 1.45 (s, 6H), 2.86–2.91 (m, 2H), 3.52 (dd, 1H, $J = 8.0$ Hz, $J = 4.0$ Hz), 3.69 (s, 3H), 3.73 (m, 1H), 3.92 (ddd, 1H, $J = 7.5$ Hz, $J = 6.0$ Hz, $J = 4$ Hz), 4.21 (dd, 1H, $J = 8.0$ Hz, $J = 6.0$ Hz), 4.38 (m, 1H), 4.62 (dd, 1H, $J = 6.0$ Hz, $J = 4.0$ Hz), 4.80 (dd, 1H, $J = 6.0$ Hz, $J_{3,4} = 4.0$ Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 24.7, 25.3, 25.7, 26.5, 33.3, 51.5, 65.2, 75.1, 77.3, 80.7, 80.8, 82.5, 109.1, 112.2, 168.7; HRMS (ESI) calcd for $C_{15}H_{24}NaO_7$: 339.1414, [M+Na]$^+$; found 339.1409.

5.4. 3,6-Anhydro-2-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*gulo*-L-*glycero*-octonic acid (3)

To a stirred solution of **2** (200 mg, 0.63 mmol) in THF (3 mL) was added 3 mL of an aqueous solution of KOH (70 mg, 1.26 mmol, 2 equiv) at room temperature. After 24 h HCl (1 N) was added until pH 3. The solution was concentrated ad half in vacuo. The product was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give **3** (190 mg, 98%) as as a colorless gum, which was used without further purification. $R_f = 0.46$ (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20} = -13$ (*c* 1.0, $CHCl_3$); IR (film) *v* 3473, 3182, 2986, 2930, 2868, 1790, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.29 (s, 3H), 1.39 (s, 3H), 1.45 (s, 6H), 2.86–3.02 (m, 2H), 3.54 (dd, 1H, $J = 8.0$ Hz, $J = 4.0$ Hz), 3.72 (m, 1H), 3.95 (ddd, 1H, $J = 7.5$ Hz, $J = 6.0$ Hz, $J = 4.0$ Hz), 4.21 (dd, 1H, $J = 8.0$ Hz, $J = 6.0$ Hz), 4.35 (m, 1H), 4.64 (dd, 1H, $J = 6.0$ Hz, $J = 4.0$ Hz), 4.79 (dd, 1H, $J = 6.0$ Hz, $J = 4.0$ Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 25.0, 25.4, 25.9, 26.8, 33.2, 66.1, 75.5, 77.3, 81.1, 81.1, 83.6, 110.0, 113.1, 176.3; HRMS (ESI) calcd for $C_{14}H_{22}NaO_7$: 325.1258, [M+Na]$^+$; found 325.1245.

5.5. Representative procedure for amide synthesis

To a stirred solution of **3** (570 mg, 1.9 mmol) in THF (2 mL) was added under argon *N,N*-carbonyldiimidazole (306 mg, 1.9 mmol) at room temperature. After 30 min, the appropriate amine was added (1.9 mmol). After stirring for 12 h under an argon atmosphere, the

solvent was removed under reduced pressure. The amide was purified by preparative high pressure column chromatography.

5.5.1. 3,6-Anhydro-2-deoxy-4,5:7,8-di-*O*-isopropylidene-*N*-[2-(1*H*-indol-3-yl)ethyl]-D-*gulo*-L-*glycero*-octonoamide (4)

Yield 80% (670 mg) as a pale yellow solid; R_f = 0.57 (CH_2Cl_2/MeOH 9:1); mp = 67–69 °C (recrystalized in hex/CH_2Cl_2); $[\alpha]_D^{20}$ = −18 (*c* 1.0, $CHCl_3$); IR (film) *v* 3333, 2980, 2930, 2874, 1706, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.24 (s, 3H), 1.40 (s, 3H), 1.43 (s, 3H), 1.47 (s, 3H), 2.63 (d, 2H, *J* = 7.5 Hz), 2.99 (t, 2H, *J* = 6.5 Hz), 3.48–3.56 (m, 2H), 3.63 (m, 1H), 3.73 (m, 1H), 3.95 (td, 1H, *J* = 7.5 Hz, *J* = 4.0 Hz), 4.21 (dd, 1H, *J* = 8.0 Hz, *J* = 6.0 Hz), 4.35 (m, 1H), 4.58 (dd, 1H, *J* = 6.0 Hz, *J* = 4.0 Hz), 4.63 (dd, 1H, *J* = 6.0 Hz, *J* = 4.0 Hz), 5.93 (t, 1H, *J* = 5.0 Hz), 7.07–7.24 (m, 3H), 7.37 (d, 1H, *J* = 7.0 Hz), 7.61 (d, 1H, *J* = 7.0 Hz), 8.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 25.1, 25.3, 26.0, 26.2, 27.2, 36.4, 40.1, 66.5, 76.1, 79.0, 81.4, 81.7, 83.9, 110.2, 111.6, 113.0, 113.1, 119.0, 119.7, 122.4, 123.2, 127.8, 136.8, 170.6; MS (ESI) calcd for $C_{24}H_{32}N_2O_6Na$: 467.2168, $[M+Na]^+$; found 467.4.

5.5.2. 3,6-Anhydro-2-deoxy-4,5:7,8-di-*O*-isopropylidene- *N*-[(2-(*R*)-hydroxy)propyl]-D-*gulo*-L-*glycero*-octonoamide (5)

Yield 75% (510 mg) as a colorless syrup; R_f = 0.55 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20}$ = −9 (*c* 1.0, $CHCl_3$); IR (film) *v* 3428, 2981, 2927, 2873, 1661 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.17 (d, 3H, *J* = 6.0 Hz), 1.28 (s, 3H), 1.38 (s, 3H), 1.44 (s, 3H), 1.46 (s, 3H), 2.63 (dd, 1H, *J* = 14.5 Hz, *J* = 7.0 Hz), 2.74 (dd, 1H, *J* = 14.5 Hz, *J* = 6.5 Hz), 3.02 (m, 1H), 3.47 (ddd, 1H, *J* = 14.0 Hz, *J* = 6.0 Hz, *J* = 3.0 Hz), 3.52 (dd, 1H, *J* = 8.0 Hz, *J* = 4.0 Hz), 3.72 (dd, 1H, *J* = 8.5 Hz, *J* = 7.0 Hz), 3.89 (ddd, 1H, *J* = 8.0 Hz, *J* = 6.0 Hz, *J* = 3.0 Hz), 3.96 (ddd, 1H, *J* = 7.0 Hz, *J* = 6.5 Hz, *J* = 3.5 Hz), 4.21 (dd, 1H, *J* = 8.5 Hz, *J* = 7.0 Hz), 4.37 (dt, 1H, *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 7.0 Hz), 4.63 (dd, 1H, *J* = 6.0 Hz, *J* = 4.0 Hz), 4.71 (dd, 1H, *J* = 6.0 Hz, *J* = 3.5 Hz), 6.47 (t, 1H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 20.9, 24.8, 25.5, 26.0, 26.9, 36.3, 47.3, 66.1, 67.2, 75.5, 78.6, 81.1, 81.6, 83.5, 110.0, 113.0, 171.5; HRMS (ESI) calcd for $C_{17}H_{29}NO_7Na$: 382.1836, $[M+Na]^+$; found 382.1834.

5.6. 3,6-Anhydro-2-deoxy-4,5:7,8-di-*O*-isopropylidene- *N*-[(2-(*R*)-acetoxy)propyl]-D-*gulo*-L-*glycero*-octonoamide (6)

To a stirred solution of **5** (206 mg, 0.57 mmol) in pyridine (6 mL) was added under argon acetic anhydride (120 mg, 1.14 mmol, 2 equiv). After stirring 12 h at room temperature, the solvent was co-evaporated with toluene and CH_2Cl_2 in vacuo. The crude product was used without further purification. Yield 95% (230 mg) as colorless liquid; R_f = 0.42 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ = +4 (*c* 1.0, $CHCl_3$); IR (film) *v* 3336, 2981, 2932, 2867, 1736, 1656 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.23 (d, 3H, *J* = 6.0 Hz), 1.28 (s, 3H), 1.38 (s, 3H), 1.43 (s, 3H), 1.45 (s, 3H), 2.06 (s, 3H), 2.66 (dd, 1H, *J* = 14.5 Hz, *J* = 7.0 Hz), 2.76 (dd, 1H, *J* = 14.5 Hz, *J* = 6.5 Hz), 3.37 (m, 1H), 3.45 (m, 1H), 3.53 (dd, 1H, *J* = 8.0 Hz, *J* = 4.0 Hz), 3.70 (dd, 1H, *J* = 8.0 Hz, *J* = 7.5 Hz), 3.94 (ddd, 1H, *J* = 7.0 Hz, *J* = 6.5 Hz, *J* = 3.5 Hz), 4.21 (dd, 1H, *J* = 8.0 Hz, *J* = 6.5 Hz), 4.36 (m, 1H), 4.62 (dd, 1H, *J* = 6.0 Hz, *J* = 4.0 Hz), 4.71 (dd, 1H, *J* = 6.0 Hz, *J* = 3.5 Hz), 5.00 (m, 1H), 6.21 (t, 1H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 17.8, 21.7, 25.2, 25.8, 26.3, 27.1, 36.2, 44.1, 66.4, 70.2, 75.9, 78.8, 81.4, 81.7, 84.0, 110.2, 113.1, 170.7, 171.1; HRMS (ESI) calcd for $C_{19}H_{31}NO_8Na$: 424.1942, $[M+Na]^+$; found 424.1940.

5.7. Representative procedure for diol synthesis

To a stirred solution of **4** or **6** (1.0 mmol) in methanol (20 mL) at 0 °C, was added an aqueous solution of 1 N HCl (7 mL). After stirring at room temperature (12 h for **5**, 6 h for **6**) was added a sat. aqueous solution of $NaHCO_3$ until pH 7. Half of the solvent was removed in vacuo. The product was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the corresponding diol used without further purification.

5.7.1. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-*N*-[2-(1*H*-indol-3-yl)ethyl]-D-*gulo*-L-*glycero*-octonoamide (7)

Yield 80% as a beige solid; R_f = 0.42 (CH_2Cl_2/MeOH 9:1); mp = 103–104 °C (recrystalized in Hex/CH_2Cl_2); $[\alpha]_D^{20}$ = −1 (*c* 1.0, $CHCl_3$); IR (film) *v* 3299, 2980, 2930, 2870, 1641 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz): δ 1.27 (s, 3H), 1.39 (s, 3H), 2.57 (d, 2H, *J* = 7.5 Hz), 2.96 (t, 2H, *J* = 6.5 Hz), 3.45–3.55 (m, 3H), 3.62 (m, 1H), 3.73 (m, 1H), 3.82 (td, 1H, *J* = 7.5 Hz, *J* = 4.0 Hz), 3.89 (m, 1H), 4.72 (dd, 1H, *J* = 6.0 Hz, *J* = 4.0 Hz), 4.76 (dd, 1H, *J* = 6.0 Hz, *J* = 4.0 Hz), 7.02 (t, 1H, *J* = 7.5 Hz), 7.10 (t, 1H, *J* = 7.5 Hz), 7.20 (s, 1H), 7.40 (d, 1H, *J* = 7.5 Hz), 7.61 (d, 1H, *J* = 7.5 Hz), 10.02 (s, 1H); ^{13}C NMR (acetone-d_6, 100.6 MHz): δ 24.5, 25.6, 25.8, 35.9, 40.0, 63.5, 71.5, 78.3, 81.4, 82.3, 82.4, 111.6, 111.7, 112.8, 118.8, 118.9, 121.5, 123.1, 128.1, 137.2, 170.1; MS calcd for $C_{21}H_{28}N_2NaO_6$: 427.18, $[M+Na]^+$: found 427.27.

5.7.2. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-*N*-[(2-(*R*)-acetoxy)propyl]-D-*gulo*-L-*glycero*-octonoamide (8)

Yield 80% as a pale yellow amorphous solid; R_f = 0.42 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20}$ = +10 (*c* 1.0, $CHCl_3$); IR (film) *v* 3369, 2986, 2943, 2878, 1728, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.23 (d, 3H, *J* = 6.5 Hz), 1.29 (s, 3H), 1.45 (s, 3H), 2.06 (1s, 3H), 2.57 (dd, 1H, *J* = 15.0 Hz, *J* = 5.0 Hz), 2.66 (dd, 1H, *J* = 15.0 Hz, *J* = 8.0 Hz), 3.32 (m, 1H), 3.43 (m, 1H), 3.58 (dd, 1H, *J* = 7.0 Hz, *J* = 3.5 Hz), 3.70 (dd, 1H, *J* = 11.0 Hz, *J* = 5.0 Hz), 3.80 (dd, 1H, *J* = 11.0 Hz, $J_{7,8'}$ = 4.0 Hz), 3.86 (m, 1H), 4.05 (m, 1H), 4.66 (dd, 1H, *J* = 6.0 Hz, *J* = 3.5 Hz), 4.72 (dd, 1H, *J* = 6.0 Hz, *J* = 3.5 Hz), 5.04 (m, 1H), 6.55 (br s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 17.9, 21.4, 24.6, 25.9, 36.2, 44.4, 66.3, 70.1, 70.7, 77.9, 81.0, 81.8, 81.9, 112.6, 170.9, 171.7; HRMS (ESI) calcd for $C_{16}H_{27}NO_8Na$: 384.1629, $[M+Na]^+$: found 384.1635.

5.8. General procedure for aldehyde synthesis

To a stirred solution of diol **7** or **8** (1.51 mmol) in methanol (32 mL), was added $NaIO_4$ (646 mg, 3.02 mmol, 2 equiv) under argon. After stirring 14 h at room temperature, the solvent was removed ad half in vacuo. The mixture was diluted with CH_2Cl_2 (80 mL). The organic layer was washed with water (3 × 10 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Aldehydes **9** and **10** were used without further purification.

5.9. General procedure for reductive amination

To a stirred solution of **9** or **10** (0.50 mmol, 1 equiv) in a mixture of methanol (7 mL) and acetic acid (0.5 mL), was added at 0 °C under argon the appropriate nucleophile (0.60 mmol, 1.2 equiv) and $NaBH_3CN$ (1.1 equiv). After 24 h at room temperature, the solvent was removed in vacuo and the mixture was diluted with CH_2Cl_2 (50 mL), washed with water (5 mL) and a satd aqueous solution of $NaHCO_3$ (2 × 5 mL) and water (5 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The compound was purified by column chromatography.

5.9.1. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[(phenyl methyl)amino]-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-*galacto*-heptonoamide (11)

Yield 55% as a colorless gum; R_f = 0.37 (AcOEt/MeOH 9:1); $[\alpha]_D^{20}$ = +11 (*c* 1.0, $CHCl_3$); IR (film) *v* 3283, 3053, 2986, 2924,

2851, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.27 (s, 3H), 1.40 (s, 3H), 2.55 (d, 2H, J = 6.5 Hz), 2.88 (t, 2H, J = 6.0 Hz), 2.98 (t, 2H, J = 6.5 Hz), 3.53–3.70 (m, 3H), 3.75 (m, 1H), 3.82 (s, 2H), 4.57 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.63 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 6.11 (t, 1H, J = 5.0 Hz), 6.99 (d, 1H, J = 2.0 Hz), 7.15–7.25 (m, 2H), 7.28 (d, 1H, J = 7.0 Hz), 7.35–7.45 (m, 5H), 7.60 (d, 1H, J = 7.0 Hz), 8.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 25.2, 25.5, 26.2, 36.7, 40.0, 48.0, 54.5, 78.4, 81.3, 81.4, 81.9, 111.6, 112.7, 113.3, 119.1, 119.3, 122.4, 122.5, 127.6, 127.8, 128.7 (2C), 128.9 (2C), 136.7, 140.4, 170.9; HRMS (ESI) calcd for $C_{27}H_{34}N_3O_4$: 464.2544, $[M+H]^+$: found 464.2539.

5.9.2. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[(pyridin-4-ylmethyl)amino]-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-*galacto*-heptonoamide (12)

Yield 55% as a colorless gum; R_f = 0.12 (AcOEt/MeOH 9:1); $[\alpha]_D^{20}$ = +13 (*c* 1.0, $CHCl_3$); IR (film) ν 3283, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.27 (s, 3H), 1.41 (s, 3H), 2.58 (d, 2H, J = 5.5 Hz), 2.86 (t, 2H, J = 6.0 Hz), 2.98 (t, 2H, J = 6.5 Hz), 3.60–3.70 (m, 3H), 3.80–3.95 (m, 3H), 4.60 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.64 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 6.10 (br s, 1H), 7.03 (s, 1H), 7.13 (t, 1H, J = 7.5 Hz), 7.20 (t, 1H, J = 7.5 Hz), 7.26 (d, 2H, J = 5.0 Hz), 7.35 (d, 1H, J = 7.5 Hz), 7.61 (d, 1H, J = 7.5 Hz), 8.54 (d, 2H, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 25.1, 25.6, 26.2, 36.6, 40.2, 48.0, 53.1, 78.4, 81.1, 81.4, 81.8, 111.6, 112.7, 113.4, 119.1, 119.8, 122.5, 123.4 (2C), 127.8, 129.2, 136.8, 149.6, 150.1 (2C), 170.7; HRMS (ESI) calcd for $C_{26}H_{33}N_4O_4$: 465.2596, $[M+H]^+$: found 465.2532.

5.9.3. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[(1*H*-benzoimidazol-2-ylmethyl)amino]-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-*galacto*-heptonoamide (13)

Yield 50% as colorless gum; R_f = 0.18 (AcOEt/MeOH 9:1); $[\alpha]_D^{20}$ = +12 (*c* 1.0, $CHCl_3$); IR (film) ν 3255, 3059, 2980, 2924, 2851, 1647 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.28 (s, 3H), 1.35 (s, 3H), 2.54 (d, 2H, J = 5.5 Hz), 2.89 (t, 2H, J = 6.0 Hz), 2.98 (t, 2H, J = 6.5 Hz), 3.43 (m, 1H), 3.52–3.70 (m, 2H), 3.75 (m, 1H), 4.07 (d, 1H, J = 15.5 Hz), 4.15 (d, 1H, J = 15.5 Hz), 4.52 (m, 1H), 4.57 (m, 1H), 6.28 (t, 1H, J = 5.0 Hz), 7.01 (s, 1H), 7.10 (t, 1H, J = 7.5 Hz), 7.16 (t, 1H, J = 7.5 Hz), 7.24 (m, 2H), 7.34 (d, 1H, J = 7.5 Hz), 7.59 (m, 3H), 9.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 25.2, 25.4, 26.2, 36.7, 40.0, 47.7, 48.1, 78.4, 81.0, 81.4, 81.9, 111.8, 112.8, 112.9, 119.0, 119.6, 122.3 (2C), 122.8 (4C), 127.8, 136.9, 154.2 (3C), 171.1; HRMS (ESI) calcd for $C_{28}H_{34}N_5O_4$: 504.2605, $[M+H]^+$: found 504.2623.

5.9.4. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[2-(1*H*-benzoimidazol-2-yl)ethylamino]-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-*galacto*-heptonoamide (14)

Yield 55% as a colorless gum; R_f = 0.12 (AcOEt/MeOH 9:1); $[\alpha]_D$ = +12 (*c* 1.0, $CHCl_3$); IR (film) ν 3234, 3051, 2927, 2851, 1648 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.29 (s, 3H), 1.38 (s, 3H), 2.55–2.55 (m, 2H), 2.95–3.00 (m, 4H), 3.05–3.15 (m, 4H), 3.50–3.55 (m, 2H), 3.66 (m, 1H), 3.82 (m, 1H), 4.58 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.64 (dd, 1H, J = 3.5 Hz, J = 6.0 Hz), 6.27 (t, 1H, J = 5.0 Hz), 7.02 (s, 1H), 7.11 (t, 1H, J = 7.5 Hz), 7.18 (t, 1H, J = 7.5 Hz), 7.22 (dd, 2H, J = 6.0 Hz, J = 3.0 Hz), 7.37 (d, 1H), 7.55–7.60 (m, 3H), 9.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 25.1, 25.5, 26.2, 28.4, 36.6, 40.1, 47.7 (2C), 78.4, 80.4, 81.4, 81.9, 111.7, 112.9, 113.1, 115.1 (2C), 119.1, 119.7, 122.4, 122.5, 122.6 (2C), 127.9, 136.9, 138.6 (2C), 154.4, 170.9; HRMS (ESI) calcd for $C_{29}H_{36}N_5O_4$: 518.2767, $[M+H]^+$: found 518.2758.

5.9.5. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[2-(pyridin-2-ylamino)ethylamino]-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-*galacto*-heptonoamide (15)

Yield 47% as a colorless gum; R_f = 0.08 (AcOEt/MeOH 9:1); $[\alpha]_D^{20}$ = +2 (*c* 1.0, $CHCl_3$); IR (film) ν 3283, 3051, 2927, 2857, 1723, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.25 (s, 3H), 1.38 (s, 3H), 2.50–2.60 (m, 2H), 2.85–2.95 (m, 4H), 2.98 (t, 2H, J = 6.0 Hz), 3.41 (t, 2H, J = 5.5 Hz), 3.45–3.60 (m, 2H), 3.65–3.75 (m, 2H), 4.53 (dd, 1H, $J_{4.5}$ = 6.0 Hz, $J_{4.3}$ = 3.5 Hz), 4.58 (dd, 1H, $J_{4.5}$ = 6.0 Hz, $J_{6.5}$ = 3.5 Hz), 5.20 (br s, 1H), 6.36 (t, 1H, J = 5.0 Hz), 6.43 (t, 1H, J = 7.5 Hz), 6.58 (dd, 1H, J = 7.5 Hz, J = 4.0 Hz), 7.07 (s, 1H), 7.10 (t, 1H, J = 7.5 Hz), 7.17 (t, 1H, J = 7.5 Hz), 7.37 (d, 1H, J = 7.5 Hz), 7.42 (m, 1H), 7.60 (d, 1H, J = 7.5 Hz), 8.07 (d, 1H, J = 4.0 Hz), 9.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 25.1, 25.4, 26.2, 36.7, 40.0, 41.6, 47.9, 49.2, 78.4, 80.9, 81.3, 81.9, 108.2, 111.8, 112.7, 113.1, 113.3, 119.1, 119.6, 122.3, 122.7, 127.9, 137.0, 138.1, 147.9, 159.0, 171.0; HRMS (ESI) calcd for $C_{27}H_{36}N_5O_4$: 494.2762, $[M+H]^+$: found 494.2786.**

5.9.6. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[2-(pyrimidin-2-ylamino)ethylamino]-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-*galacto*-heptonoamide (16)

Yield 45% as a colorless gum; R_f = 0.08 (AcOEt/MeOH 9:1); $[\alpha]_D^{20}$ = +3 (*c* 1.0, $CHCl_3$); IR (film) ν 3288, 3045, 2927, 2857, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.26 (s, 3H), 1.39 (s, 3H), 2.50–2.55 (m, 2H), 2.85–2.90 (m, 4H), 2.99 (t, 2H, J = 6.0 Hz), 3.50–3.65 (m, 4H), 3.59 (m, 1H), 3.68 (m, 1H), 4.56 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.60 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 5.66 (t, 1H, J = 5.0 Hz), 6.33 (t, 1H, J = 5.0 Hz), 6.55 (t, 1H, J = 5.0 Hz), 7.09 (s, 1H), 7.11 (t, 1H, J = 7.5 Hz), 7.19 (t, 1H, J = 7.5 Hz), 7.38 (d, 1H, J = 7.5 Hz), 7.60 (d, 1H, J = 7.5 Hz) , 8.28 (d, 2H, J = 5.0 Hz), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 25.1, 25.4, 26.2, 36.8, 40.0, 41.1, 47.9, 49.2, 78.5, 81.1, 81.3, 81.9, 111.1, 111.7, 112.7, 113.3, 119.1, 119.7, 122.4, 122.6, 127.9, 136.9, 158.5 (2C), 162.7, 171.0; HRMS (ESI) calcd for $C_{26}H_{35}N_6O_4$: 495.2720, $[M+H]^+$: found 495.2722.

5.9.7. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[2-(*N*-benzyloxycarbonylamino)ethylamino]-L-*galacto*-heptono-*N*-[2-(1*H*-indol-3-yl)ethyl]-amide (17)

Yield 50% as a colorless gum; R_f = 0.12 (AcOEt/MeOH 9:1); $[\alpha]_D^{20}$ = +7 (*c* 1.5, $CHCl_3$); IR (film) ν 3315, 2927, 1704, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.24 (s, 3H), 1.39 (s, 3H), 2.00 (br s, 1H), 2.56 (d, 2H, J = 6.5 Hz), 2.70–2.75 (m, 2H), 2.80 (d, 2H, J = 6.0 Hz), 2.96 (t, 2H, J = 6.5 Hz), 3.20–3.25 (m, 2H), 3.44 (m, 1H), 3.50–3.65 (m, 2H), 3.76 (m, 1H), 4.55–4.60 (m, 2H), 5.11 (s, 2H), 5.40 (t, 1H, J = 5.0 Hz), 6.18 (t, 1H, J = 5.0 Hz), 7.02 (d, 1H, J = 2.0 Hz), 7.10 (td, 1H, J = 7.5 Hz, J = 2.0 Hz), 7.18 (td, 1H, J = 7.5 Hz, J = 2.0 Hz), 7.25–7.40 (m, 6H), 7.59 (d, 1H, J = 7.5 Hz), 8.82 (s, 1H); RMN ^{13}C ($CDCl_3$, 100.6 MHz): δ 24.9, 25.3, 26.0, 36.4, 39.9, 40.6, 47.6, 49.1, 66.9, 78.1, 80.9, 81.1, 81.6, 111.5, 112.5, 113.0, 118.9, 119.5, 122.2, 122.4, 127.6, 128.3 (3C), 128.7 (2C), 136.6, 136.7, 156.9, 171.0; HRMS (ESI) calcd for $C_{30}H_{39}N_4O_6$: 551.2864, $[M+H]^+$: found 551.2859.

5.9.8. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[(pyridin-4-ylmethyl)amino]-*N*-[(2-(*R*)-acetoxy)propyl]-L-*galacto*-heptonoamide (18)

Yield 25% as a colorless gum; R_f = 0.10 (AcOEt/MeOH 9:1); $[\alpha]_D^{20}$ = +13 (*c* 1.0, $CHCl_3$); IR (film) ν 3294, 2932, 1734, 1656 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.21 (d, 3H, J = 6.0 Hz), 1.30 (s, 3H), 1.43 (s, 3H), 2.01 (1s, 3H), 2.28 (br s, 1H), 2.61 (d, 2H, J = 5.0 Hz), 2.91 (d, 2H, J = 6.5 Hz), 3.35–3.50 (m, 2H), 3.68 (td, 1H, J = 6.5 Hz, J = 3.0 Hz), 3.84 (d, 1H, J = 5.0 Hz), 3.90 (s, 2H), 4.63–4.70 (m, 2H), 4.97 (m, 1H), 6.31 (t, 1H, J = 6.0 Hz), 7.27 (d, 2H, J = 6 Hz), 8.52 (d, 2H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 17.8, 21.4, 25.0, 26.0, 36.4, 44.1, 47.9, 52.9, 70.1, 78.3, 81.0, 81.3, 81.6, 112.5, 123.2 (2C), 149.4, 149.9 (2C), 170.7, 170.9; HRMS (ESI) calcd for $C_{21}H_{32}N_3O_6$: 422.2286, $[M+H]^+$: found 422.2287.

5.9.9. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[1*H*-benzoimidazol-2-ylmethyl)amino]-*N*-[(2-(*R*)-acetoxy)propyl-L-*galacto*-heptonoamide (19)

Yield 45% as a colorless gum; R_f = 0.12 (AcOEt/MeOH 9:1); $[\alpha]_D^{20}$ = +21 (*c* 1.0, $CHCl_3$); IR (film) *v* 3261, 3061, 2986, 2927, 1734, 1658 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.23 (d, 3H, *J* = 6.0 Hz), 1.37 (s, 3H), 1.43 (s, 3H), 2.05 (1s, 3H), 2.61 (dd, 1H, *J* = 15.0 Hz, *J* = 5.0 Hz), 2.66 (dd, 1H, *J* = 14.0 Hz, *J* = 7.0 Hz), 2.99 (dd, 1H, *J* = 12.5 Hz, *J* = 5.5 Hz), 3.08 (dd, 1H, *J* = 12.5 Hz, *J* = 7.0 Hz), 3.37 (m, 1H), 3.46 (m, 1H), 3.67 (ddd, 1H, *J* = 7.0 Hz, *J* = 5.5 Hz, *J* = 4.0 Hz), 3.93 (ddd, 1H, *J* = 7.0 Hz, *J* = 5.0 Hz, *J* = 3.5 Hz), 4.14 (d, 1H, *J* = 16.0 Hz), 4.25 (d, 1H, *J* = 16.0 Hz), 4.69 (dd, 1H, *J* = 6.0 Hz, *J* = 4.0 Hz), 4.75 (dd, 1H, *J* = 6.0 Hz, *J* = 3.5 Hz), 5.02 (m, 1H), 6.29 (t, 1H, *J* = 6.0 Hz), 7.24 (dd, 2H, *J* = 6.0 Hz, *J* = 3.0 Hz), 7.58 (dd, 2H, *J* = 6.0 Hz, *J* = 3.0 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 18.0, 21.6, 25.4, 26.3, 36.5, 44.4, 47.9, 48.2, 70.4, 78.4, 81.0, 81.6, 81.8, 112.9, 115.5 (2C), 122.6 (2C), 138.7, 154.4 (2C), 171.0, 171.4; HRMS (ESI) calcd for $C_{23}H_{33}N_4O_6$: 461.2395, $[M+H]^+$: found 461.2389.

5.9.10. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[2-(1*H*-benzoimidazol-2-yl)ethylamino]-*N*-[(2-(*R*)-acetoxy)propyl]-L-*galacto*-heptonoamide (20)

Yield 50% as a colorless gum; R_f = 0.10 (AcOEt/MeOH 9:1); $[\alpha]_D^{20}$ = +15 (*c* 1.0, $CHCl_3$). IR (film) *v* 3256, 2986, 2943, 1734, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.20 (d, 3H, *J* = 6.0 Hz), 1.33 (s, 3H), 1.42 (s, 3H), 2.06 (s, 3H), 2.61 (d, 2H, *J* = 6.5 Hz), 2.66 (dd, 1H, *J* = 14.0 Hz, *J* = 7.0 Hz), 3.02 (d, 2H, *J* = 6.0 Hz), 3.05–3.15 (m, 4H), 3.35–3.45 (m, 2H), 3.67 (td, 1H, *J* = 6.0 Hz, *J* = 3.0 Hz), 3.93 (td, 1H, *J* = 6.5 Hz, *J* = 3.0 Hz), 4.65–4.60 (m, 2H), 4.95 (m, 1H), 6.37 (t, 1H, *J* = 6.0 Hz), 7.18 (dd, 2H, *J* = 6.0 Hz, *J* = 3.0 Hz), 7.52 (dd, 2H, *J* = 6.0 Hz, *J* = 3.0 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 17.8, 21.4, 25.0, 26.0, 28.6, 36.2, 44.1, 47.7 (2C), 70.1, 78.1, 80.6, 81.4, 81.6, 112.7, 114.9 (2C), 122.1 (2C), 138.5, 154.7 (2C), 170.7, 171.0; HRMS (ESI) calcd for $C_{24}H_{35}N_4O_6$: 475.2551, $[M+H]^+$: found 475.2521.

5.9.11. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7[2-(pyridin-2-ylamino)ethylamino]-*N*-[(2-(*R*)-acetoxy)propyl]-L-*galacto*-heptonoamide (21)

Yield 15% as a colorless gum; R_f = 0.22 (AcOEt/MeOH 2:1); $[\alpha]_D^{20}$ = +15 (*c* 1.0, $CHCl_3$); IR (film) *v* 3321, 3067, 2927, 1731, 1658 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.22 (d, 3H, *J* = 6.0 Hz), 1.29 (s, 3H), 1.42 (s, 3H), 2.03 (s, 3H), 2.39 (br s, 1H), 2.57 (dd, 1H, *J* = 13.5 Hz, *J* = 4.5 Hz), 2.65 (dd, 1H, *J* = 13.5 Hz, *J* = 6.0 Hz), 2.94 (m, 4H), 3.30–3.45 (m, 4H), 3.66 (td, 1H, *J* = 6.0 Hz, *J* = 3 Hz), 3.93 (td, 1H, *J* = 7.0 Hz, *J* = 3.0 Hz), 4.60–4.70 (m, 2H), 4.98 (m, 1H), 5.08 (br s, 1H), 6.40 (d, 1H, *J* = 8.5 Hz), 6.45 (t, 1H, *J* = 6.0 Hz), 6.55 (dd, 1H, *J* = 6.5 Hz, *J* = 5.0 Hz), 7.39 (ddd, 1H, *J* = 8.5 Hz, *J* = 6.5 Hz, *J* = 2.0 Hz), 7.58 (dd, 1H, *J* = 5.0 Hz, *J* = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 17.8, 21.4, 25.0, 26.0, 36.4, 41.6, 44.0, 47.8, 49.0, 70.1, 78.2, 81.0, 81.3, 81.6, 107.4, 112.5, 112.9, 137.5, 148.2, 159.0, 170.8, 171.0; HRMS (ESI) calcd for $C_{22}H_{35}N_4O_6$: 451.2551, $[M+H]^+$: found 451.2525.

5.9.12. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[2-(*N*-benzyloxycarbonylamino)ethylamino]-*N*-[(2-(*R*)-acetoxy)propyl]-L-*galacto*-heptonoamide (22)

Yield 75% as a colorless gum; R_f = 0.14 (AcOEt/MeOH 9:1); $[\alpha]_D^{20}$ = +10 (*c* 0.7, $CHCl_3$); IR (film) *v* 3315, 2976, 2933, 2868, 1715, 1656 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.21 (d, 3H, *J* = 6 Hz), 1.29 (s, 3H), 1.44 (s, 3H), 2.04 (s, 3H), 2.56–2.65 (m, 2H), 2.75–2.95 (m, 4H), 3.23–3.45 (m, 4H), 3.62 (m, 1H), 3.86 (m, 1H), 4.61–4.70 (m, 2H), 4.96 (m, 1H), 5.10 (s, 2H), 5.38 (br s, 1H), 5.50 (br s, 1H), 6.27 (br s, 1H), 7.30–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 17.5, 21.2, 24.7, 25.8, 36.1, 43.9, 47.5, 49.0, 50.5, 66.6, 69.9, 77.9, 80.8, 81.1, 81.4, 112.3, 127.7, 128.0 (2C), 128.5 (2C), 136.6, 156.5, 170.6, 170.8; HRMS (ESI) calcd for $C_{25}H_{38}N_3O_8$: 508.2653, $[M+H]^+$: found 508.2641.

5.9.13. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[(phenylmethyl)amino]-*N*-[(2-(*R*)-hydroxy)propyl]-L-*galacto*-heptonoamide (23)

Yield 40% (for two steps) as a colorless gum; R_f = 0.10 (AcOEt/MeOH 9:1); $[\alpha]_D^{20}$ = +5 (*c* 0.8, $CHCl_3$); IR (film) *v* 3315, 2927, 2852, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.08 (d, 3H, *J* = 6.5 Hz), 1.25 (s, 3H), 1.40 (s, 3H), 2.52 (dd, 1H, *J* = 15.5 Hz, *J* = 6.0 Hz), 2.61 (dd, 1H, *J* = 15.5 Hz, J_2 = 9.0 Hz), 2.87 (d, 2H, *J* = 6.0 Hz), 2.95 (m, 1H), 3.37 (ddd, 1H, *J*= 13.5 Hz, *J* = 6.5 Hz, *J* = 3.0 Hz), 3.62 (td, 1H, *J* = 6.0 Hz, *J* = 3.0 Hz), 3.75 (s, 2H), 3.78–3.88 (m, 2H), 4.58–4.65 (m, 2H), 6.69 (t, 1H, *J* = 5.5 Hz), 7.25–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 21.0, 24.9, 26.0, 36.4, 47.2, 47.8, 54.1, 66.7, 78.2, 80.7, 81.4, 81.6, 112.5, 127.3, 128.4 (2C), 128.6 (2C), 139.6, 171.7; HRMS (ESI) calcd for $C_{20}H_{31}N_2O_5$: 379.2227, $[M+H]^+$: found 379.2226.

5.10. General procedure for acetate deprotection

To a solution of amides **18–22** (0.15 mmol) in methanol (6 mL) was added a catalytic amount of sodium. The mixture was stirred for 20 min at room temperature. Amberlite IR-120 was added until pH 4 and then filtered. The solvent was removed under reduced pressure. When necessary, the compound was purified by column chromatography.

5.10.1. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[(pyridin-4-ylmethyl)amino]-*N*-[(2-(*R*)-hydroxy)propyl]-L-*galacto*-heptonoamide (24)

Yield 70% as a colorless gum; R_f = 0.24 (AcOEt/MeOH 2:1); $[\alpha]_D^{20}$ = −9 (*c* 1.0, $CHCl_3$); IR (film) *v* 3315, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.18 (d, 3H, *J* = 6.5 Hz), 1.32 (s, 3H), 1.46 (s, 3H), 2.56 (dd, 1H, *J* = 14.5 Hz, *J* = 5.0 Hz), 2.66 (dd, 1H, *J* = 14.5 Hz, *J* = 8.5 Hz), 2.96 (d, 2H, *J* = 6.0 Hz), 3.05 (ddd, 1H, *J* = 13.5 Hz, *J* = 8.0 Hz, *J* = 6.0 Hz), 3.43 (ddd, 1H, *J* = 13.5 Hz, *J* = 6.0 Hz, *J* = 3.0 Hz), 3.76 (td, 1H, *J* = 6.5 Hz, *J* = 3.5 Hz), 3.88–3.96 (m, 4H), 4.64–4.69 (m, 2H), 6.72 (t, 1H, *J* = 6.0 Hz), 7.34 (d, 2H, *J* = 5.5 Hz), 8.57 (d, 2H, *J* = 5.5 Hz); ^{13}C NMR (MeOH-d_4, 62.9 MHz): δ 21.0, 25.0, 26.3, 30.9, 36.5, 47.9, 52.7, 67.4, 79.6, 80.7, 82.7, 83.1, 113.6, 125.3 (2C), 149.4, 150.4 (2C), 173.6; HRMS (ESI) calcd for $C_{19}H_{30}N_3O_5$: 380.2180, $[M+H]^+$: found 380.2183.

5.10.2. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[1*H*-benzoimidazol-2-ylmethyl)amino]-*N*-[(2-(*R*)-hydroxy)propyl]-L-*galacto*-heptonoamide (25)

Yield : 85% as a colorless gum; R_f = 0.35 (AcOEt/MeOH 2:1); $[\alpha]_D^{20}$ = +7 (*c* 1.0, $CHCl_3$); IR (film) *v* 3288, 2981, 2932, 1648 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.29 (d, 3H, *J* = 6.5 Hz), 1.30 (s, 3H), 1.39 (s, 3H), 2.51 (dd, 1H, *J* = 14.0 Hz, *J* = 3.5 Hz), 2.66 (dd, 1H, *J* = 14.0 Hz, *J* = 10.0 Hz), 2.87 (m, 1H), 2.95–3.05 (m, 2H), 3.60–3.71 (m, 2H), 3.88 (dt, 1H, *J* = 10.0 Hz, *J* = 3.0 Hz), 4.06 (m, 1H), 4.13 (s, 2H), 4.62 (dd, 1H, *J* = 6.0 Hz, *J* = 4.0 Hz), 4.68 (dd, 1H, *J* = 6.0 Hz, *J* = 3.0 Hz), 6.74 (br s, 1H), 7.24 (dd, 2H, *J* = 6.0 Hz, *J* = 3.0 Hz), 7.57 (dd, 2H, *J* = 6.0 Hz, *J* = 3.0 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 21.0, 24.8, 26.0, 36.8, 47.4, 47.8, 48.6, 66.1, 78.6, 80.7, 81.5, 81.6, 112.8, 115.1 (2C), 122.6 (2C), 138.5, 153.1 (2C), 171.9; HRMS (ESI) calcd for $C_{21}H_{31}N_4O_5$: 419.2289, $[M+H]^+$: found 419.2289.

5.10.3. 3,6-Anhydro-2-deoxy- -4,5-*O*-isopropylidene-7-[2-(1*H*-benzoimidazol-2-yl)ethylamino]-*N*-[(2-(*R*)-hydroxy)propyl]-L-*galacto*-heptonoamide (26)

Yield 80% as a colorless gum; R_f = 0.20 (AcOEt/MeOH 3:2); $[\alpha]_D^{20}$ = 0° (*c* 1.0, $CHCl_3$); IR (film) *v* 3283, 2981, 2932, 1648 cm^{-1};

^{1}H NMR (MeOH-d_4, 250 MHz): δ 1.15 (d, 3H, J = 6.5 Hz), 1.29 (s, 3H), 1.40 (s, 3H), 2.59 (dd, 1H, J = 14.0 Hz, J = 6.0 Hz), 2.67 (dd, 1H, J = 14.0 Hz, J = 7.0 Hz), 3.04 (d, 2H, J = 6.0 Hz), 3.10–3.25 (m, 6H), 3.74 (td, 1H, $J_{6.7}$ = 6.0 Hz, $J_{5.6}$ = 3.0 Hz), 3.78–3.87 (m, 1H), 3.88 (ddd, 1H, J = 7.0 Hz, J = 6.0 Hz, J = 3.0 Hz), 4.71 (dd, 1H, J = 5.0 Hz, J = 3.0 Hz), 4.74 (dd, 1H, J = 5.0 Hz, J = 3.0 Hz), 7.22 (dd, 2H, J = 6.0 Hz, J = 3.0 Hz), 7.54 (dd, 2H, J = 6.0 Hz, J = 3.0 Hz); ^{13}C NMR (MeOH-d_4, 62.9 MHz): δ 21.0, 24.9, 26.2, 29.4, 36.6, 45.3, 47.8, 48.5, 67.4, 79.5, 81.1, 82.7, 83.0, 113.5, 115.6 (2C), 123.4 (2C), 139.6, 154.5 (2C), 173.6; HRMS (ESI) calcd for $C_{22}H_{33}N_4O_5$: 433.2445, $[M+H]^+$: found 433.2445.

5.10.4. 3,6-Anhydro-2-deoxy–4,5-*O*-isopropylidene-7[2-(pyridin-2-ylamino)ethylamino]-*N*-[(2-(*R*)-hydroxy)propyl]-L-*galacto*-heptonoamide (27)

Yield 82% as a colorless gum; R_f = 0.15 (AcOEt/MeOH 2:1); $[\alpha]_D^{20}$ = +10 (c 1.0, $CHCl_3$); IR (film) ν 3310, 1650 cm^{-1}; ^{1}H NMR (MeOH-d_4, 400 MHz): δ 1.16 (d, 3H, J = 6.5 Hz), 1.32 (s, 3H), 1.44 (s, 3H), 2.60–2.72 (m, 2H), 3.05 (dd, 2H, J = 11.0 Hz, J = 5.5 Hz), 3.13 (d, 2H, J = 6.0 Hz), 3.15 (dd, 1H, J = 13.5 Hz, J = 6.5 Hz), 3.21 (dd, 1H, J = 13.5 Hz, J = 5.0 Hz), 3.50 (t, 2H, J = 6.0 Hz), 3.78 (td, 1H, J = 6.0 Hz, J = 3.5 Hz), 3.84 (m, 1H), 3.99 (ddd, 1H, J = 7.5 Hz, J = 6.0 Hz, J= 3.5 Hz), 4.74 (dd, 1H, J = 6.0 Hz, J= 3.5 Hz), 4.77 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 6.60 (m, 2H), 7.47 (ddd, 1H, J = 8.5 Hz, J = 7.0 Hz, J = 2.0 Hz), 7.98 (m, 1H); ^{13}C NMR (MeOH-d_4, 100.6 MHz): δ 21.0, 24.9, 26.3, 36.5, 41.4, 47.8, 48.4, 50.4, 67.4, 79.6, 80.2, 82.6, 83.0, 110.5, 113.6, 113.7, 139.1, 147.9, 160.4, 173.5; HRMS (ESI) calcd for $C_{20}H_{33}N_4O_5$: 409.2445, $[M+H]^+$: found 409.2444.

5.11. General procedure for carbamate deprotection

To a solution of **17** or **22** (80 mg, 0.145 mmol) in methanol (6 mL) was added Pd/C (10%) (15% w/w). The mixture was stirred under H_2 atmosphere. After 24 h the reaction mixture was filtered through a pad of Celite and the solvent removed in vacuo.

5.11.1. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[2-(amino)ethylamino]-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-*galacto*-heptonoamide (28)

Yield 90% as a colorless liquid; R_f = 0.08 (AcOEt/MeOH 2:1); $[\alpha]_D^{20}$ = +8 (c 1.0, $CHCl_3$); IR (film) ν 3251, 2976, 2933, 2857, 1645 cm^{-1}; ^{1}H NMR (MeOH-d_4, 250 MHz): δ 1.30 (s, 3H), 1.44 (s, 3H), 2.59 (m, 2H), 2.85–3.00 (m, 8H), 3.51 (m, 2H), 3.61 (m, 1H), 3.86 (m, 1H), 4.62 (m, 1H), 4.69 (m, 1H), 7.00 (td, 1H, J = 7.5 Hz, J = 1.0 Hz), 7.06 (td, 1H, J = 7.5 Hz, J = 1.0 Hz), 7.10 (s, 1H), 7.37 (br d, 1H, J = 7.5 Hz), 7.59 (br d, 1H, J = 7.5 Hz); ^{13}C NMR (MeOH-d_4, 62.9 MHz): δ 25.1, 26.3, 26.4, 36.7, 40.3, 41.6, 45.5, 47.2, 79.5, 81.7, 82.6, 83.0, 112.4 (2C), 113.4, 119.5, 119.7, 122.5, 123.7, 128.9, 138.2, 173.3; HRMS (ESI) calcd for $C_{22}H_{33}N_4O_4$: 417.2496, $[M+H]^+$: found 417.2523.

5.11.2. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[2-(amino)ethylamino]-*N*-[(2-(*R*)-acetoxy)propyl]-L-*galacto*-heptonoamide (29)

Yield 99% as a colorless gum; R_f = 0.08 (AcOEt/MeOH 2:1); $[\alpha]_D^{20}$ = −26 (c 1.0, $CHCl_3$); IR (film) ν 3277, 2981, 2933, 2873, 1734, 1650 cm^{-1}; ^{1}H NMR (MeOH-d_4, 250 MHz): δ 1.20 (d, 3H, J = 6.0 Hz), 1.31 (s, 3H), 1.44 (s, 3H), 2.03 (1s, 3H), 2.57–2.65 (m, 2H), 2.82–2.97 (m, 4H), 3.23–3.45 (m, 4H), 3.66 (m, 1H), 3.91 (m, 1H), 4.67–4.77 (m, 2H), 4.96 (m, 1H); ^{13}C NMR (MeOH-d_4, 62.9 MHz): δ 17.9, 21.3, 25.1, 26.4, 36.5, 41.4, 44.6, 49.0, 51.9, 71.0, 79.4, 81.6, 82.7, 83.1, 113.4, 172.5, 173.6; HRMS (ESI) calcd for $C_{17}H_{32}N_3O_6$: 374.2286, $[M+H]^+$: found 374.2285.

5.12. Generale procedure for guanidinylation

To a stirred solution of amine **28** or **29** (45 mg, 0.108 mmol) in DMF (3 mL) was added *N,N′*-bis(dibenzyloxycarbonyl)-*S*-methylisothiourea 17 (77 mg, 0.216 mmol, 2 equiv), $HgCl_2$ (29 mg, 0.108 mmol, 1 equiv) and Et_3N (33 mg, 0.324 mmol, 3 equiv) under argon at room temperature. After stirring for 14 h at room temperature, the solvent was removed in vacuo and the residue was dissolved in EtOAc (40 mL). The organic layer was washed with water (5 mL) and brine (5 mL) and then dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The compounds were purified by column chromatography.

5.12.1. 3,6-Anhydro-2-deoxy-*N*-[2-(1*H*-indol-3-yl)ethyl]-4,5-*O*-isopropylidene-7-[[*N*-[bis[(phenylmethoxy) carbonyl]]amino-iminomethyl]-*N*-[2-[bis[(phenylmethoxy)carbonyl]]guanidinoethyl]amino]-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-*galacto*-heptonoamide (30)

Yield 35% (40 mg) as a colorless gum; R_f = 0.62 (AcOEt); $[\alpha]_D^{20}$ = +12 (c 1.0, $CHCl_3$); IR (film) ν 3349, 2924, 2853, 1734, 1643 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.24 (s, 3H), 1.27 (s, 3H), 2.30–2.42 (m, 2H), 2.75–3.00 (m, 2H), 3.22–3.36 (m, 2H), 3.50–3.70 (m, 6H), 3.78 (m, 1H), 3.90 (m, 1H), 4.30–4.38 (m, 2H), 5.05 (s, 2H), 5.12 (s, 2H), 5.19 (s, 4H), 6.95 (d, 1H, J = 2.0 Hz), 7.04–7.18 (m, 2H), 7.26–7.38 (m, 20H), 7.42 (m, 1H), 7.55 (d, 1H, J = 7.5 Hz), 8.45 (br s, 1H), 9.04 (br s, 1H), 9.50 (br s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 24.8, 26.0, 29.9, 36.4 (2C), 39.6 (3C), 67.4 (2C), 68.0, 68.5, 78.7, 79.2, 80.7, 82.0, 111.6, 112.2, 112.7, 118.7, 119.2, 121.9, 123.0, 127.7, 128.3 (4C), 128.6 (4C), 128.7 (4C), 128.9 (4C), 129.0 (4C), 134.8 (2C), 136.7, 136.8 (2C), 153.7 (2C), 156.5 (2C), 163.6 (2C), 170.1; HRMS (ESI) calcd for $C_{56}H_{61}N_8O_{12}$: 1037.4392, $[M+H]^+$: found 1037.4390.

5.12.2. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[[*N*-[bis[(phenylmethoxy)carbonyl]]aminoiminomethyl]-*N*-[2-[bis[(phenylmethoxy)carbonyl]]guanidinoethyl] amino]-*N*-[(2-(*R*)-acetoxy)propyl]-L-*galacto*-heptonoamide (31)

Yield 25% (30 mg) as a colorless gum; R_f = 0.51 (AcOEt); $[\alpha]_D^{20}$ = −2 (c 0.7, $CHCl_3$); IR (film) ν 3332, 2981, 2938, 1734, 1642, 1618 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21 (d, 3H, J = 6.0 Hz), 1.21 (s, 3H), 1.33 (s, 3H), 2.04 (1s, 3H), 2.50 (d, 2H, J = 6.0 Hz), 3.36 (m, 1H), 3.43 (m, 1H), 3.55–3.70 (m, 6H), 3.87 (m, 1H), 3.96 (m, 1H), 4.35–4.45 (m, 2H), 4.96 (m, 1H), 5.10 (s, 4H), 5.16 (s, 4H), 6.05 (br s, 1H), 7.35–7.40 (m, 20H), 8.49 (br s, 1H), 9.34 (br s, 1H), 11.63 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 17.9, 21.6, 25.1, 26.1, 36.4, 39.1, 44.2, 48.0, 49.5, 67.6 (2C), 68.7 (2C), 70.2, 78.9, 79.2, 81.1, 81.8, 113.0, 128.5 (2C), 128.7 (4C), 128.9 (4C), 128.9 (4C), 129.1 (4C), 129.2 (2C), 135.0 (2C), 137.0 (2C), 153.9 (2C), 156.7 (2C), 163.9 (2C), 170.5, 171.0; HRMS (ESI) calcd for $C_{51}H_{60}N_7O_{14}$: 994.4198, $[M+H]^+$: found 994.4187.

5.13. General procedure for carbamate deprotection

To a solution of **30** or **31** (30 mg, 0.04 mmol) in methanol (2 mL) was added Pd/C (10%) (15% w/w). The mixture was stirred under H_2 atmosphere. After 24 h, the reaction mixture was filtered through a pad of Celite and the solvent removed in vacuo. The mixture was purified by column chromatography on C18 silica gel (eluent H_2O/CH_3CN 7/3 with 0.1% of TFA) and the product was lyophilized.

5.13.1. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[*N*-(aminoiminomethyl)-*N*-(2-guanidinoethyl)amino]-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-*galacto*-heptonoamide (32)

Yield 90% (13 mg) as a white solid; R_f = 0.24 (H_2O/CH_3CN/TFA 6:4:0.1); $[\alpha]_D^{20}$ = +9 (c 0.3, MeOH); IR (film) ν 3363, 2927, 2851,

1672 cm^{-1}; ^1H NMR (MeOH-d_4, 400 MHz): δ 1.32 (s, 3H), 1.47 (s, 3H), 2.52–2.66 (m, 2H), 2.96 (t, 2H, J = 7 Hz), 3.36–3.42 (m, 2H), 3.43–3.65 (m, 6H), 3.75 (m, 1H), 3.92 (ddd, 1H, J = 8.0 Hz, J = 5.5 Hz, J = 3.5 Hz), 4.69 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.77 (dd, 1H, J = 6 Hz, J = 3.5 Hz), 7.02 (t, 1H, J = 7.5 Hz), 7.07–7.12 (m, 2H), 7.35 (d, 1H, J = 7.5 Hz), 7.58 (d, 1H, J = 7.5 Hz); ^{13}C NMR (MeOH-d_4, 62.9 MHz): δ 23.8, 23.9, 25.2, 35.5, 39.6, 40.5, 48.9, 49.1, 78.8, 79.4, 81.3, 81.9, 111.3, 112.2, 112.7, 118.3, 118.6, 121.3, 122.5, 127.8, 137.1, 158.3, 159.5, 172.0; HRMS (ESI) calcd for $C_{24}H_{37}N_8O_4$: 501.2932, $[M+H]^+$: found 501.2943.

5.13.2. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[[*N*-(aminoiminomethyl)-*N*-(2-guanidinoethyl)]amino]-*N*-[(2-(*R*)-hydroxy)propyl]-L-*galacto*-heptonoamide (33)

Yield 90% (11 mg) as white solid; R_f = 0.35 (H_2O/CH_3CN/TFA 6:4:0.1); $[\alpha]_D^{20}$ = −5 (c 0.5, MeOH). IR (film) ν 3342, 2976, 2927, 1674 cm^{-1}; ^1H NMR (MeOH-d_4, 400 MHz): δ 1.17 (d, 3H, J = 6.0 Hz), 1.34 (s, 3H), 1.49 (s, 3H), 2.61–2.72 (m, 2H), 3.14 (dd, 1H, J = 13.5 Hz, J = 7.0 Hz), 3.25 (dd, 1H, J = 13.5 Hz, J = 5.0 Hz), 3.52 (t, 2H, J = 6.0 Hz), 3.60–3.71 (m, 4H), 3.79–3.87 (m, 2H), 4.00 (m, 1H), 4.76 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.82 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz); ^{13}C NMR (MeOH-d_4, 100.6 MHz): δ 19.9, 23.7, 25.2, 35.3, 38.7, 46.7, 48.7, 49.6, 66.4, 78.9 (2C), 81.2, 81.9, 112.8, 157.8, 158.2, 172.4; HRMS (ESI) calcd for $C_{17}H_{34}N_7O_5$: 416.2621, $[M+H]^+$: found 416.2622.

5.14. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[(2-hydroxy)ethylamino]-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-*galacto*-heptonoamide (34)

To a stirred solution of **9** (400 mg, 1.075 mmol, 1 equiv) in methanol (20 mL), was added under argon 3-aminopropanol (197 mg, 3.225 mmol, 3 equiv), NEt_3 (1.075 mmol, 1 equiv), Ti(i-PrO)$_4$ (catalytic amount) and 4 Å molecular sieves (80 mg). After stirring at room temperature for 20 h, $NaBH_4$ (1.1 equiv) was added at 0 °C and stirred at room temperature for 2 h. The solvent was then removed in vacuo and the mixture was diluted with CH_2Cl_2 (50 mL), washed with water (5 mL) and a sat. aqueous solution of $NaHCO_3$ (2 x 5 mL) and water (5 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The compound was purified by column chromatography. Yield 45% (200 mg) as a colorless gum; R_f = 0.10 (AcOEt/MeOH 2:1); $[\alpha]_D^{20}$ = +7 (c 0.5, $CHCl_3$); IR (film) ν 3297, 2986, 2934, 2857, 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.23 (s, 3H), 1.39 (s, 3H), 2.52 (m, 2H), 2.70–2.98 (m, 8H), 3.42–3.68 (m, 3H), 3.73 (td, 1H, J = 6.5 Hz, J = 3.5 Hz), 4.49 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.54 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 6.25 (t, 1H, J = 5.5 Hz), 7.01 (s, 1H), 7.08 (ddd, 1H, J = 8.0 Hz, J = 1.0 Hz), 7.16 (ddd, 1H, J = 8.0 Hz, J = 1.0 Hz), 7.36 (br d, 1H, J = 8.0 Hz), 7.56 (br d, 1H, J = 7.5 Hz), 9.10 (br s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 24.7, 25.0, 25.8, 36.2, 39.7, 47.7, 51.3, 60.7, 77.9, 80.8, 81.0, 81.4, 111.3, 112.2, 112.6, 118.6, 119.2, 121.9, 122.3, 127.4, 136.5, 170.6; HRMS (ESI) calcd for $C_{22}H_{31}N_3NaO_5$: 440.2156, $[M+Na]^+$: found 440.2156 .

5.15. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[3-[*N*-[bis[(*tert*-butyloxy)carbonyl]]aminoiminomethyl]-2-oxo-1-imidazolidinyl]-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-*galacto*-heptonoamide (35)

To a solution of C-glycoside **34** (160 mg, 0.384 mmol) *N*,*N*′,*N*″-tri-(*tert*-butoxycarbonyl)guanidine (413 mg, 1.1 mmol) and PPh_3 (151 mg, 0.58 mmol) in dry THF (10 mL) at 0 °C under argon was added dropwise *via* syringe diethyl azodicarboxylate (98 μL, 0.58 mmol) over 5 min. The reaction was stirred at room temperature for 18 h. The solvent was evaporated in vacuo. The compound was purified by column chromatography. Yield 35% (85 mg) as a white solid; R_f = 0.34 (AcOEt); $[\alpha]_D^{20}$ = +8 (c 0.4, $CHCl_3$); IR (film) ν 3320, 2975, 2932, 2873, 1763, 1709, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.24 (s, 3H), 1.38 (s, 3H), 1.50 (s, 18H), 2.50 (dd, 1H, J = 13.5 Hz, J = 3.5 Hz), 2.58 (dd, 1H, J = 13.5 Hz, J = 5.5 Hz), 2.94 (t, 2H, J = 6.5 Hz), 3.20–3.53 (m, 6H), 3.60–3.80 (m, 4H), 4.50–4.60 (m, 2H), 6.24 (t, 1H, J = 5.5 Hz), 7.01 (d, 1H, J = 2.0 Hz), 7.05 (t, 1H, J = 7.5 Hz), 7.14 (t, 1H, J = 7.5 Hz), 7.35 (d, 1H, J = 7.5 Hz), 7.55 (d, 1H, J = 7.5 Hz), 9.12 (br s, 1H), 10.54 (br s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 24.7, 25.2, 25.8, 28.10 (6C), 36.1, 40.1, 41.1, 42.3, 42.8, 78.0, 78.2 (2C), 79.3, 80.6, 81.4, 111.4, 112.6, 112.7, 118.6, 119.1, 121.8, 122.4, 127.4, 136.5, 144.7 (2C), 156.7 (2C), 170.2; HRMS (ESI) calcd for $C_{34}H_{48}N_6NaO_9$: 707.3375, $[M+Na]^+$: found 707.3411.

5.16. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[3-[*N*-(aminoiminomethyl)]-2-oxo-1-imidazolidinyl-*N*-[2-(1*H*-indol-3-yl)ethyl]]-L-*galacto*-heptonoamide (36)

To a stirred solution of **35** (70 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added 1 mL of TFA at 0 °C. After stirring for 14 h at room temperature, the solvent was removed in vacuo and coevaporated with Et_2O to remove residual TFA. The residue was chromatographed on C18 silica gel (eluent H_2O/CH_3CN 7:3 with 0.1% of TFA) and the product was lyophilized. Yield 72% (35 mg) as a white solid; R_f = 0.26 (H_2O/CH_3CN/TFA 6:4:0.1); $[\alpha]_D^{20}$ = +8 (c 0.6, MeOH); IR (film) ν 3353, 2986, 2932, 1739, 1681 cm^{-1}; ^1H NMR (MeOH-d_4, 250 MHz): δ 1.27 (s, 3H), 1.43 (s, 3H), 2.51 (dd, 1H, J = 13.0 Hz, J = 4.0 Hz), 2.59 (dd, 1H, J = 13.0 Hz, J = 6.0 Hz), 2.92 (t, 2H, J = 7.0 Hz), 3.39–3.80 (m, 9H), 3.86 (ddd, 1H, J = 7.5 Hz, J = 5.5 Hz, J = 3.5 Hz), 4.61 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.68 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 6.99 (ddd, 1H, J = 8 Hz, J = 7 Hz, J = 1 Hz), 7.06 (s, 1H), 7.07 (ddd, 1H, J = 8.0 Hz, J = 7.0 Hz, J = 1 Hz), 7.32 (d, 1H, J = 7.0 Hz), 7.55 (d, 1H, J = 8.0 Hz); ^{13}C NMR (MeOH-d_4, 62.9 MHz): δ 23.4, 24.8 (2C), 35.2, 40.0 (2C), 41.7, 42.7, 78.1, 78.6, 81.0, 81.5, 110.8, 111.9, 112.2, 117.9, 118.2, 120.9, 122.1, 127.4, 136.7, 154.9, 155.1, 171.7; HRMS (ESI) calcd for $C_{24}H_{33}N_6O_5$: 485.2512, $[M+H]^+$: found 485.2503.

5.17. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[*N*-[2-[bis[(*tert*-butyloxy)carbonyl]]guanidinoethyl]amino]-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-*galacto*-heptonoamide (37)

Prepared using the general procedure of reductive amination. Yield 40% as a white solid; R_f = 0.14 (AcOEt/MeOH 9:1); $[\alpha]_D^{20}$ = +9 (c 0.4, $CHCl_3$); IR (film) ν 3326, 2975, 2932, 1720, 1642 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.24 (s, 3H), 1.37 (s, 3H), 1.45 (s, 9H), 1.50 (s, 9H), 2.48 (m, 1H), 2.60 (m, 1H), 2.60–2.80 (m, 4H), 2.97 (t, 2H, J = 6.5 Hz), 3.32–3.50 (m, 4H), 3.56–3.70 (m, 2H), 4.52 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.57 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 6.32 (br t, 1H, J = 5.5 Hz), 7.03–7.16 (m, 3H), 7.36 (br d, 1H, J = 7.5 Hz), 7.58 (br d, 1H, J = 7.5 Hz), 8.61 (br t, 1H, J = 5.0 Hz), 9.20 (br s, 1H), 11.54 (br s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 24.8, 25.2, 25.9, 28.2 (3C), 28.3 (3C), 36.4, 39.8, 40.5, 47.4, 48.3, 77.9, 79.5, 81.0, 81.2, 81.6, 83.3, 111.5, 112.3, 112.8, 118.7, 119.2, 121.9, 122.2, 127.6, 136.6, 153.3, 156.4, 163.6, 170.7; HRMS (ESI) calcd for $C_{33}H_{51}N_6O_8$: 659.3763, $[M+H]^+$: found 659.3724.

5.18. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[*N*-[2-[bis[(*tert*-butyloxy)carbonyl]]guanidinoethyl]amino]-*N*-[(2-(*R*)-acetoxy)propyl]-L-*galacto*-heptonoamide (38)

Prepared using general procedure of reductive amination. Yield 40% as a white solid; R_f = 0.11 (AcOEt/MeOH 9:1); $[\alpha]_D^{20}$ = −5 (c 0.3, $CHCl_3$); IR (film) ν 3349, 2979, 2934, 1732, 1645, 1592 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.24 (s, 3H), 1.30 (s, 3H), 1.46 (s, 9H), 1.49 (s, 9H), 2.05 (s, 3H), 2.52–2.66 (m, 2H), 2.96 (t, 2H, J = 6.5 Hz), 3.30–3.70 (m, 6H), 3.80–4.00 (m, 2H), 4.60–4.75 (m,

2H), 4.98 (m, 1H), 6.29 (br t, 1H, J = 6.0 Hz), 7.91 (br s, 1H), 8.62 (br s, 1H), 11.47 (br s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 17.5, 21.2, 24.8, 25.8, 28.2 (3C), 28.4 (3C), 36.2, 40.3, 40.7, 47.3, 48.3, 69.9, 77.9, 78.1, 78.3, 81.0, 81.2, 81.4, 112.3, 153.0, 156.2, 163.5, 170.5, 171.1; MS (ESI) calcd for $C_{28}H_{49}N_5O_{10}$: 615.3479, $[M+H]^+$: found 616.4.

5.19. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-[*N*-[2-guanidinoethyl]amino]-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-*galacto*-heptonoamide (39)

To a stirred solution of **37** (70 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added 1 mL of TFA at 0 °C. After stirring for 14 h at room temperature, the solvent was removed in vacuo and coevaporated with Et_2O. The residue was chromatographed on C18 silica gel (eluant H_2O/CH_3CN 7:3 with 0.1% of TFA) and the product was lyophilized. Yield 80% (30 mg) as a white solid; R_f = 0.31 (H_2O/CH_3CN/TFA 6:4:0.1); $[\alpha]_D^{20}$ = +10 (c 0.8, MeOH); IR (film) ν 3348, 2986, 2922, 2852, 1669 cm^{-1}; ^{1}H NMR (MeOH-d_4, 250 MHz): δ 1.29 (s, 3H), 1.44 (s, 3H), 2.60 (m, 2H), 2.95 (t, 2H, J = 7 Hz), 3.22–3.28 (m, 2H), 3.34–3.58 (m, 6H), 3.82–3.96 (m, 2H), 4.69 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.76 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 6.99 (ddd, 1H, J = 8.0 Hz, J = 7.0 Hz, J = 1.0 Hz), 7.05–7.12 (m, 2H), 7.33 (br d, 1H, J = 7.0 Hz), 7.56 (br d, 1H, J = 8.0 Hz); ^{13}C NMR (MeOH-d_4, 62.9 MHz): δ 23.2, 24.6, 24.7, 34.8, 37.4, 40.1, 46.2, 46.7, 76.1, 78.6, 80.8, 81.6, 110.8, 111.8, 112.6, 117.8, 118.2, 120.9, 122.0, 127.4, 136.7, 157.6, 171.6. HRMS (ESI) calcd for $C_{23}H_{35}N_6O_4$: 459.2714, $[M+H]^+$: found 459.2762.

5.20. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7[*N*-[2-guanidinoethyl]amino]-*N*-[(2-(*R*)-acetoxy)propyl]-L-*galacto*-heptonoamide (40)

To a stirred solution of **38** (80 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added 1 mL of TFA at 0 °C. After stirring for 14 h at room temperature, the solvent was removed in vacuo and coevaporated with Et_2O. The residue was chromatographed on C18 silica gel (eluant H_2O/CH_3CN 7/3 with 0.1% of TFA) and the product was lyophilized. Yield 38% (20 mg) as a white solid; R_f = 0.31 (H_2O/CH_3CN/TFA 6:4:0.1); $[\alpha]_D^{20}$ = −3 (c 0.3, MeOH); IR (film) ν 3347, 3181, 2992, 2938, 1672 cm^{-1}; ^{1}H NMR (MeOH-d_4, 250 MHz): δ 1.20 (d, 3H, J = 6.5 Hz), 1.31 (s, 3H), 1.45 (s, 3H), 2.04 (s, 3H), 2.63 (m, 2H), 3.16–3.26 (m, 2H), 3.32–3.39 (m, 2H), 3.41–3.49 (m, 2H), 3.60 (t, 2H, J = 6 Hz), 3.89 (dt, 1H, J = 9 Hz, J = 3 Hz), 4.00 (td, 1H, J = 6.5 Hz, J = 3 Hz), 4.73–4.82 (m, 2H), 4.92–5.05 (m, 1H); ^{13}C NMR (MeOH-d_4, 62.9 MHz): δ 17.7, 21.2, 24.7, 26.1, 36.0, 38.9, 44.7, 47.6, 48.2, 70.9, 77.6, 80.0, 82.3, 83.0, 114.0, 159.0, 172.8, 173.4; HRMS (ESI) calcd for $C_{18}H_{34}N_5O_6$: 416.2504, $[M+H]^+$: found 416.2470.

5.21. 3,6-Anhydro-2-deoxy-4,5-O-isopropylidene-7-(L-arginyl methyl ester)-*N*-[2-(1H-indol-3-yl)ethyl]-L-galacto-heptonoamide (41)

Prepared using the general procedure of reductive amination with L-arginine methyl ester. Yield 75% as a white solid; R_f = 0.34 (H_2O/CH_3CN/TFA 6:4:0.1); $[\alpha]_D^{20}$ = +10 (c 0.9, $CHCl_3$); IR (film) ν 3353, 3180, 2991, 2943, 2884, 1747, 1669 cm^{-1}; ^{1}H NMR (MeOH-d_4, 400 MHz): δ 1.32 (s, 3H), 1.47 (s, 3H), 1.64 (m, 1H), 1.74 (m, 1H), 1.93–2.10 (m, 2H), 2.57–2.67 (m, 2H), 2.97 (t, 2H, J = 7.0 Hz), 3.24 (t, 2H, J = 7.0 Hz), 3.36 (m, 1H), 3.43–3.58 (m, 3H), 3.86 (m, 1H), 3.87 (s, 3H), 3.96 (ddd, 1H, J = 7.5 Hz, J = 6.0 Hz, J = 3.5 Hz), 4.19 (dd, 1H, J = 7.5 Hz, J = 5.0 Hz), 4.73 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.79 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 7.02 (ddd, 1H, J = 8.0 Hz, J = 7.0 Hz, J = 1 Hz), 7.09 (s, 1H), 7.11 (ddd, 1H, J = 8.0 Hz, J = 7.0 Hz, J = 1 Hz), 7.35 (d, 1H, J = 7.0 Hz), 7.59 (d, 1H, J = 8.0 Hz); ^{13}C NMR (MeOH-d_4, 62.9 MHz): δ 23.3, 24.2, 24.7, 24.8, 26.2, 34.9, 40.1, 40.3, 45.5, 52.4, 59.3, 76.3, 78.6, 81.0, 81.6, 110.8, 111.8, 112.6, 117.8, 118.2, 120.9, 122.0, 127.4, 136.7, 157.3, 169.1, 171.7; HRMS (ESI) calcd for $C_{27}H_{41}N_6O_6$: 545.3082, $[M+H]^+$: found 545.3087.

5.22. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-(L-arginyl methyl ester)-*N*-[(2-(*R*)-acetoxy)propyl]-L-*galacto*-heptonoamide (42)

Prepared using the general procedure of reductive amination with L-arginine methyl ester. Yield 68% as a white solid; R_f = 0.37 (H_2O/CH_3CN/TFA 6:4:0.1); $[\alpha]_D^{20}$ = +6 (c 0.2, MeOH); IR (film) ν 3347, 3164, 2986, 2943, 1736, 1658 cm^{-1}; ^{1}H NMR (MeOH-d_4MeOH-d_4, 250 MHz): δ 1.21 (d, 3H, J = 6.5 Hz), 1.31 (s, 3H), 1.45 (s, 3H), 1.60–1.80 (m, 2H), 1.90–2.05 (m, 2H), 2.05 (s, 3H), 2.63 (d, 2H, J = 6.5 Hz), 3.24 (m, 4H), 3.35–3.45 (m, 2H), 3.84 (m, 1H), 3.87 (s, 3H), 3.99 (td, 1H, J = 6.5 Hz, J = 3.5 Hz), 4.13 (dd, 1H, J = 7.0 Hz, J = 5.5 Hz), 4.75 (dd, 1H, J = 6 Hz, J = 3.5 Hz), 4.80 (m, 1H), 5.00 (m, 1H); ^{13}C NMR (MeOH-d_4, 62.9 MHz, 62.9 MHz): δ 16.3, 19.8, 23.3, 24.2, 24.7, 26.4, 34.6, 40.3, 43.3, 45.6, 52.4, 59.4, 69.5, 76.3, 78.5, 81.0, 81.6, 112.6, 157.3, 169.2, 171.3, 172.0; HRMS (ESI) calcd for $C_{22}H_{40}N_5O_8$: 502.2871, $[M+H]^+$: found 502.2886.

5.23. General procedure for saponification

To a stirred solution of **41** and **42** (0.11 mmol) in THF/H_20 (6 mL/2 mL) was added LiOH (3 equiv for **41**, 5 equiv for **42**). After stirring for 14 h at room temperature, a solution of HCl (3 N) was added dropwise until pH 6–7. The solvent was removed in vacuo and the residue was chromatographed on C18 silica gel (eluant H_2O/CH_3CN 7:3 with 0.1% of TFA) and the product was freeze dried.

5.23.1. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-(L-arginyl)-*N*-[2-(1*H*-indol-3-yl)ethyl]-L-*galacto*-heptonoamide (43)

Yield 68% as a white solid; R_f = 0.44 (H_2O/CH_3CN/TFA 6:4:0.1); $[\alpha]_D^{20}$ = +13 (c 1.0, MeOH); IR (film) ν 3353, 3185, 2986, 2932, 2852, 1696, 1664 cm^{-1}; ^{1}H NMR (MeOH-d_4, 400 MHz): δ 1.32 (s, 3H), 1.47 (s, 3H), 1.68 (m, 1H), 1.82 (m, 1H), 1.92–2.09 (m, 2H), 2.62 (m, 2H), 2.97 (t, 2H, J = 7.5 Hz), 3.24 (t, 2H, J = 7.0 Hz), 3.36–3.59 (m, 4H), 3.87 (dt, 1H, J = 8.0 Hz, J = 3.0 Hz), 3.96 (td, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.01 (dd, 1H, J = 7.0 Hz, J = 5.0 Hz), 4.73 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.80 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 7.02 (t, 1H, J = 7.5 Hz), 7.09 (s, 1H), 7.10 (t, 1H, J = 7.5 Hz), 7.35 (d, 1H, J = 7.5 Hz), 7.58 (d, 1H, J = 7.5 Hz); ^{13}C NMR (MeOH-d_4, 62.9 MHz): δ 23.6, 24.7, 25.1, 25.2, 26.5, 35.2, 40.6, 40.7, 45.8, 60.1, 76.3, 79.0, 81.4, 82.1, 111.3, 112.2, 113.1, 118.2, 118.6, 121.3, 122.4, 127.8, 137.2, 157.7, 170.3, 172.1; HRMS (ESI) calcd for $C_{26}H_{39}N_6O_6$: 531.2926, $[M+H]^+$: found 531.2905.

5.23.2. 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-7-(L-arginyl)-*N*-[(2-(*R*)-hydroxy)propyl]-L-*galacto*-heptonoamide (44)

Yield 87% as a white solid; R_f = 0.60 (H_2O/CH_3CN/TFA 6:4:0.1); $[\alpha]_D^{20}$ = +5 (c 0.4, MeOH); IR (film) ν 3358, 3185, 2981, 2943, 2884, 1674 cm^{-1}; ^{1}H NMR (MeOH-d_4, 400 MHz): δ 1.17 (d, 3H, J = 6.5 Hz), 1.33 (s, 3H), 1.48 (s, 3H), 1.62 (m, 1H), 1.70–1.96 (m, 3H), 2.60–2.74 (m, 2H), 3.10–3.30 (m, 3H), 3.34–3.44 (m, 2H), 3.60 (m, 1H), 3.68 (m, 1H), 3.82–3.92 (m, 2H), 4.02 (m, 1H), 4.78 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz), 4.82 (dd, 1H, J = 6.0 Hz, J = 3.5 Hz); ^{13}C NMR (MeOH-d_4, 62.9 MHz): δ 19.6, 23.2, 24.5, 24.7, 26.6, 34.9, 40.4, 45.6, 46.4, 46.6, 65.9, 76.0, 78.5, 81.1, 81.7, 112.6, 157.3, 171.9, 172.1; HRMS (ESI) calcd for $C_{19}H_{36}N_5O_7$: 446.2609, $[M+H]^+$: found 446.2626.

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