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Synthesis and biological evaluation of novel neamine–nucleoside conjugates potentially targeting to RNAs

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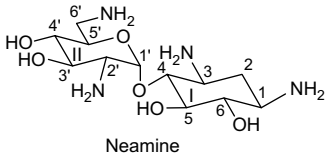
ABSTRACT

Eighteen novel neamine–nucleoside conjugates with ethylenediamine–lysine or ethylenediamine–arginine as the linker were synthesized and their potential binding to A site of 16S RNA and TAR RNA was evaluated using SPR (surface plasmon resonance). Compared with neamine, compounds **10i** and **10q** show 6.3 and 4.8 times potential in binding to A site of 16S RNA and eight and six times potential in binding to TAR RNA, respectively. According to the data of SPR, it indicates that amino acid residue and nucleobase moieties of the designed neamine–nucleosides conjugates exhibit the important contributions for the binding to A site of 16S RNA and TAR RNA. The molecular docking study on the interaction between the ligands and A site of 16S RNA is in agreement with the experimental data. The novel type of modification may provide a promising way for the development of neamine derivatives effectively targeting to RNAs.

1. Introduction

With the research advances in the clearance of RNA structure and its important function in the life cycle of pathogenic microorganisms and the processing of diseases, RNA has been viewed as an important small molecular drug target for finding potential drugs.[1,2] Aminoglycoside antibiotic family including neomycin, kanamycin, paramomycin, and so on has been known to bind potentially to many important RNAs such as bacterial A site of 16S rRNA,[3,4] HIV-1 transactivation response element (TAR) RNA,[5] HIV-1 Rev responsive element (RRE) RNA,[6] group I introns,[7] and the hammerhead ribozyme.[8] But the high toxicity, which mainly resulted from the nonspecific electrostatic interactions limited their clinic use at a large degree,[9] and also, aminoglycosides are prone to lead to drug resistance because of their own structural instability and the modification of aminoglycoside-modifying enzymes.[10] The detailed study has shown that neamine (Fig. 1), as the common part of neomycin-class aminoglycosides, is the minimum motif that can specifically bind to the A site of 16S RNA and affect the translation procedure in protein synthesis.[4] It seems a promising way to keep the neamine core and develop novel potential neamine derivatives. Up to now, many efforts have been made to optimize the core structure neamine, among which neamine–peptide or nucleobase conjugates have been proved to be a convenient and effective strategy to improve the binding to RNAs. The neamine conjugates with arginine/lysine,[11,12] arginine peptide,[13] nucleobase,[14] aromatic rings,[15] peptide nucleic acid,[16] and alkylamines[17] can enhance its binding affinity and some of them have been showed certain binding selectivity. Until now there are no general rules for the design of the specific as well as potential RNA-binding small molecules, and all of the reported aminoglycoside conjugates were designed by connecting neamine with peptide or nucleobase directly to one of amino groups on the aminosugar moiety.



Neamine

Figure 1. Structure of neamine.

Previously, two types of neamine–nucleoside conjugates were synthesized from our group by the condensation of azidodisaccharide and nucleoside using ethylenediamine as a linker. Results from the data of SPR evaluation suggested that the nucleobase played a significant role to bind to A site of 16S RNA and an ethylenediamine

Abbreviations: Ac, acetyl; Arg, argnine; BAIB, [bis(acetoxy)-iodo]benzene; BOC, *tert*-butoxycarbonyl; DCC, dicyclohexylcarbodiimide; DMF, *N*,*N*-dimethyl formamide; DMSO, dimethyl sulfoxide; Eda, ethylenediamine; Et, ethyl; Fmoc, 9-fluorenylmethyloxycarbonyl; HOBT, 1-hydroxybenzotriazole; Lys, lysine; Pbf, 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl; Py, pyridine; TEMPO, 2,2,4,6-tetramethyl-1-piperidinyloxyl; rt, room tempreture; THF, tetrahydrofuranyl; Tf_2O, trifluoromethanesulfonic anhydride.

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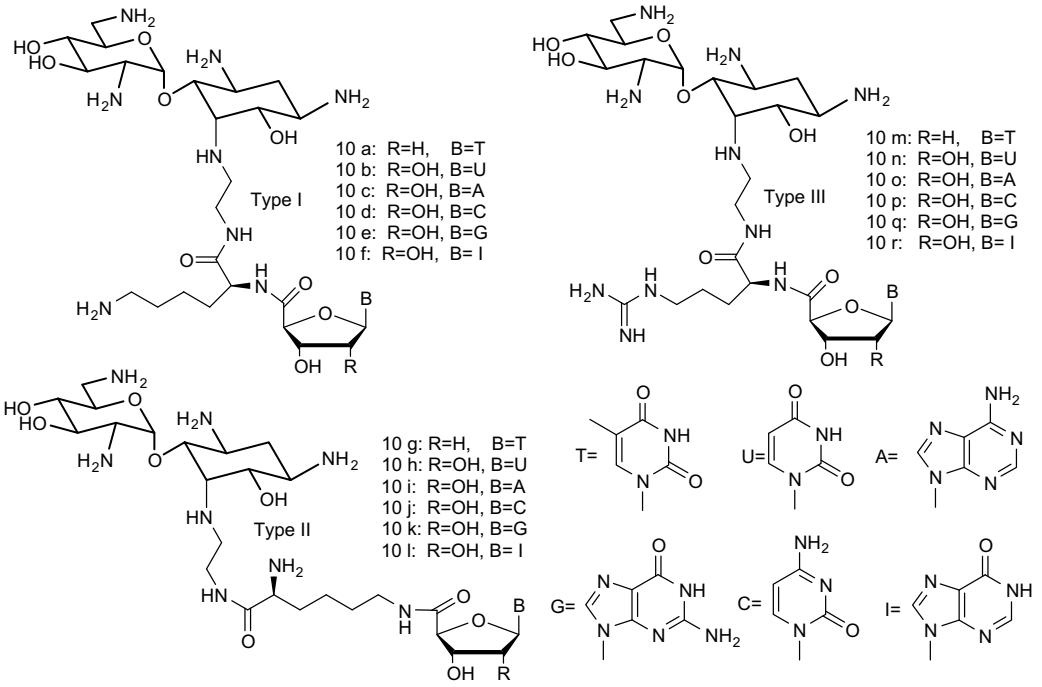


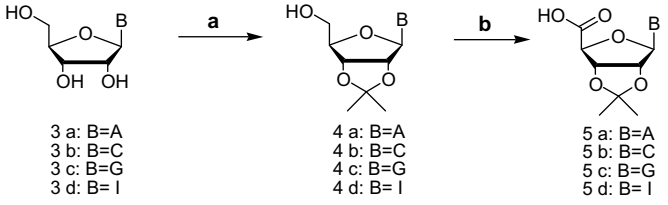
Figure 2. Structures of neamine–nucleoside conjugates.

linker between the neamine and nucleoside was favorable for this binding.[18] In this report we prepared a new class of neamine–nucleoside conjugates (Fig. 2), in which an ethylenediamine–amino acid was used as linker for the modification of the 5-hydroxyl group of neamine by nucleosides. The amino groups on neamine play an important role in their binding to the target RNAs. Keeping the amino group free in the neamine molecule and modification of other positions of neamine may lead the derivatives contributing a various interaction to RNA. Compounds **10a**–**r** were designed using a flexible side chain to connect the neamine and nucleosides, which were expected to recognize the specific site of RNA. Moreover, lysines and arginines are often present in the RNA-binding proteins (for example, HIV-1 transactiviting (Tat) proteins and regulator of expression of virion (Rev) proteins),[19,20] neamine–arginine and neamine–lysine conjugates both enhance the inhibition of HIV-1 TAR-Tat interaction compared with their mother compound neamine.[11] Based on these backgrounds, three types of neamine–nucleoside conjugates were synthesized: *type I* (compounds **10a**–**f**) consists in neamine derivatives with ethylenediamine–lysine as the linker and nucleosides connecting at the α-NH_2 group of lysine; *type II* (compounds **10g**–**l**) is the similar structure as type II but the nucleosides are condensed with the ε-NH_2 group of lysine; *type III* (compounds **10m**–**r**) is formed by a number of neamine derivatives with ethylenediamine–arginine as the linker and nucleoside connecting at the α-NH_2 group of arginine. The interactions between compounds **10a**–**r** with the A site of 16S RNA and TAR RNA were evaluated by dissociation constants (K_D values in μM) using SPR method. The dissociation constants clearly indicated that three types of neamine–nucleoside conjugates showed the better binding properties to 16S RNA and TAR RNA than the neamine derivatives reported previously.[18]

2. Results and discussion

2.1. Synthesis of neamine–nucleoside conjugates 10a–r

Six protected 5′-carboxylic acid-nucleosides **2a**, **b**, **5a**–**d** were synthesized (Scheme 1, Fig. 3), among which **2a** and **2b** were

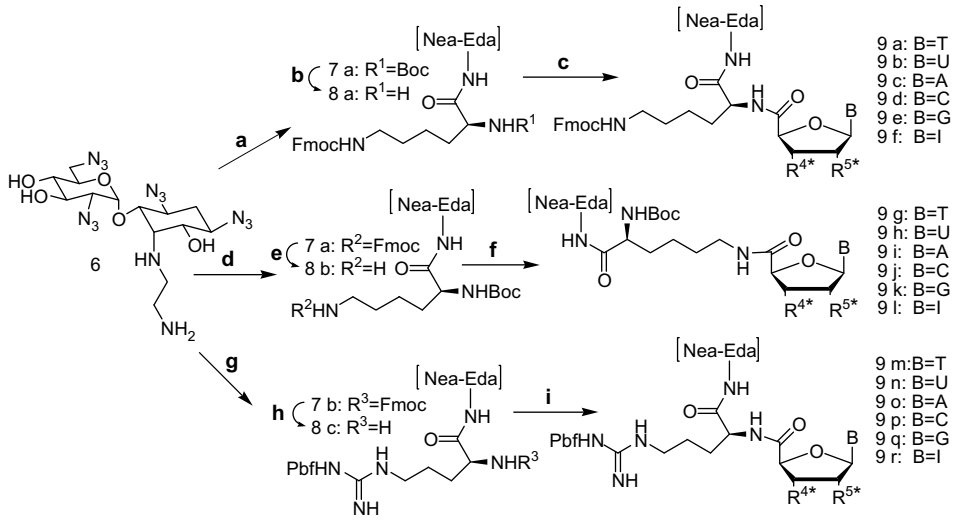


Scheme 1. Synthesis of protected 5′-carboxylic acid-nucleosides **5a**, **5b**, **5c**, and **5d**. Reagents and conditions: (a) CH_3COCH_3, 70% $HClO_4$, rt; (b) BAIB, TEMPO, CH_3CN, H_2O, rt.

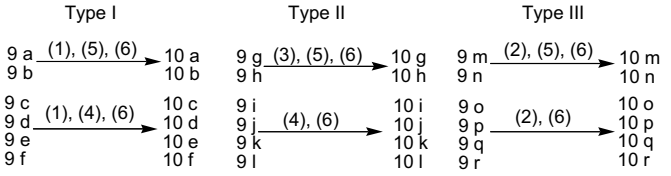
Figure 3. Structures of protected 5′-carboxylic acid-nucleosides **2a** and **2b**.

prepared from compounds **1a** and **1b** according to the published procedures.[18] Compounds **5a**, **5b**, **5c**, and **5d** were synthesized from the nucleosides **3a**–**d**. After the protection of 2′- and 3′-hydroxyl group by isopropylidene group, the nucleoside intermediates **4a**, **4b**, **4c**, and **4d** were obtained in good yield. Compounds **4a**–**d** were oxidized by BAIB and TEMPO in mild conditions to afford the desired 5′-carboxylic acid-nucleosides **5a**, **5b**, **5c**, and **5d** in 75–82% yields.

For the synthesis of compounds of types I–III (Schemes 2 and 3), compound **6** was prepared by the reported procedure and used as the starting material.[18] Compounds **8a** and **8b** were synthesized by the condensation reaction of compound **6** with Boc-Lys(Fmoc)-OH to give compound **7a** first. For compound **8a**, the Boc-protection group on α-NH_2 group of lysine was selectively removed by CF_3COOH in CH_2Cl_2 (1:4) and compound **8b** was obtained by the removal of Fmoc-protection group on ε-NH_2 group of lysine moiety using Et_2NH in DMF (1:9). Compound **6** was condensed with Fmoc-Arg(Pbf)-OH to yield **7b**, after the removal of the Fmoc group on the α-NH_2 group of arginine using the same procedure as the



Scheme 2. Synthesis of protected neamine–nucleoside conjugates. Reagents and conditions: (a) Boc-Lys(Fmoc)-OH, HOBt, DCC, DMF, 0 °C to rt; (b) CF_3COOH/CH_2Cl_2 (1:4), rt; (c) 5′-carboxylic acid-nucleoside (**2a**, **2b**, **5a**, **5b**, **5c**, and **5d**), HOBt, DCC, DMF, 0 °C to rt; (d) Boc-Lys(Fmoc)-OH, HOBt, DCC, DMF, 0 °C to rt; (e) Et_2NH/DMF (1:9), rt; (f) 5′-carboxylic acid-nucleoside (**2a**, **2b**, **5a**, **5b**, **5c**, and **5d**), HOBt, DCC, DMF, 0 °C to rt; (g) Fmoc-Arg(Pbf)-OH, HOBt, DCC, DMF, 0 °C to rt; (h) Et_2NH/DMF (1:9), rt; (i) 5′-carboxylic acid-nucleoside (**2a**, **2b**, **5a**, **5b**, **5c**, and **5d**), HOBt, DCC, DMF, 0 °C to rt. *Note*: (1) [Nea-Eda] represents the structure of compound **6**; (2) for the nucleoside part, when B=T, R^{4*}=OAc, R^{5*}=H; when B=U, R^{4*}=R^{5*}=OAc, and when B=A, C, G, and I, R^{4*} and R^{5*} represents the isopropylidene protection of nucleoside 2′- and 3′-hydroxyl group.



Scheme 3. Synthesis of neamine–nucleoside conjugates. Reagents and conditions: (1) Et_2NH/DMF (1:9), rt; (2) $CF_3COOH/H_2O/PhSCH_3$ (94:3:3), rt; (3) CF_3COOH/CH_2Cl_2 (1:4), rt; (4) CF_3COOH/H_2O (9:1), 0 °C; (5) NH_3/CH_3OH, 0 °C. (6) H_2S, pyridine/Et_3N/H_2O (4:3:2), rt.

preparation of compound **8b**, compound **8c** was obtained in 85% yield. Compounds **8a**, **8b**, and **8c** were condensed with the protected 5′-carboxylic acid-nucleosides **2a**, **b** and **5a**–**d**, respectively, to provide compounds **9a**–**r** in 70–82% yields.

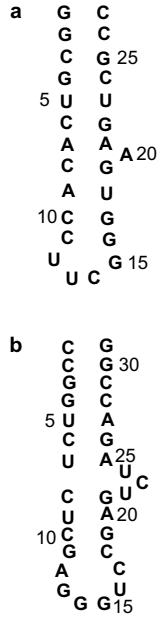


Figure 4. (a) Structure of A site of 16S RNA, (b) structure of TAR RNA.

Three types of desired products **10a**–**r** were obtained in good yields after removal of all the protection groups (Scheme 3). The target molecules **10a**–**r** were purified by reversed-phase HPLC (1‰ CF_3COOH in H_2O and CH_3OH) and obtained as the appropriate trifluoroacetic salts. The intermediates and final products were characterized by ^1H NMR, ^{13}C NMR, HRMS, and optical rotations.

2.2. RNA-binding assay and molecular docking study

The binding properties of the neamine–nucleoside conjugates **10a**–**r** to the A site of 16S RNA and TAR RNA (Fig. 4a and b) were evaluated by the determination of dissociation constants using SPR Biacore 3000 instrument,[21,22] and the dissociation constants (K_D values in μM) were listed in Table 1. The dissociation constants clearly indicate that (1) three types of neamine–nucleoside conjugates show the better binding properties to 16S RNA and TAR RNA than the neamine derivatives reported previously.[18] It indicates that the amino acid–ethylenediamine linker in these compounds

Table 1
The K_D values of neamine–nucleoside conjugates binding to A site of 16S and TAR RNA

Comp	K_D (16S) μM	K_D (TAR) μM
Neamine	19	24
10a	35	46
10b	39	49
10c	14	12
10d	16	29
10e	18	21
10f	23	27
10g	13	19
10h	13	27
10i	3	3
10j	18	21
10k	9	15
10l	9	11
10m	14	13
10n	14	12
10o	7	9
10p	12	10
10q	4	4
10r	13	5

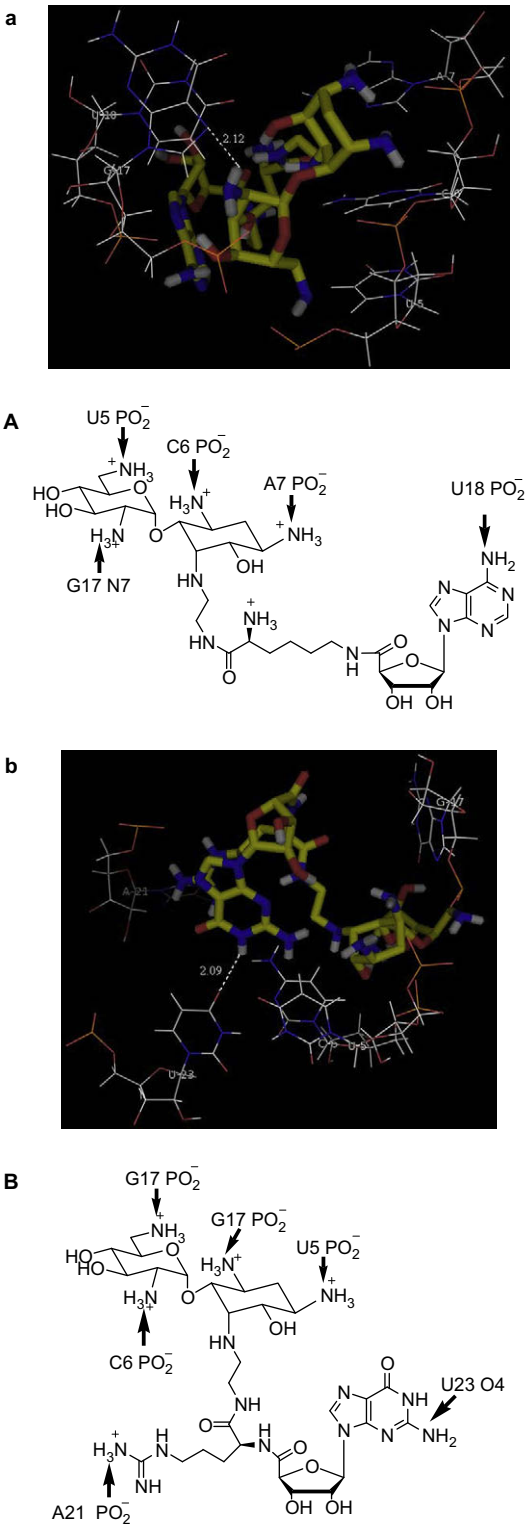


Figure 5. Molecular modeling for the interactions between **10i** (a, A), **10 q** (b, B) and A site of 16S RNA. Panel (a) and (b) shows the hydrogen bonds only and panel (A) and (B) indicates the interactions including all the hydrogen bonds and electrostatic interactions.

could increase the binding affinities. (2) Compounds of types II and III show the binding properties with equal to or better than the parent neamine (for A site of 16S RNA, the dissociation constants K_D of compounds of type II are 3–18 μM and type III are 4–14 μM and for TAR RNA compounds of type II, K_D=3–27 μM and type III K_D=4–13 μM, respectively). It seems that the ε-amino side chain of lysine in the structure of the compound of type I does not exhibit the contribution for the interaction with RNA and the guanidino group of arginine side chain exhibits more contributions in this interaction. (3) Interestingly, all of the compounds consisting of adenine or guanine (**10c**, **10g**, **10i**, **10k** and **10o**, **10q**) indicate the better K_D values than the others, among which **10i** and **10q** showed the K_D values of 6.3 and 4.8 times potential in binding to 16S RNA and eight and six times potential in binding to TAR RNA, respectively (3 and 4 μM to A site of 16S RNA and TAR RNA, respectively). It exhibits that the nucleobase could play an important role in the recognition of the designed compounds and target RNA.

To obtain more information about the interaction between the neamine–nucleoside conjugates and the A site of 16S RNA, molecular docking study of **10i** and **10q** was investigated.[23] The structure of A site of 16S RNA fragment was extracted from the protein databank (PDB code 1PBR) and the software AutoDock 3.0 was used for the molecular docking calculation of two neamine derivatives. By computer calculation, the final configuration (Fig. 5a and b) with the lowest docking energy was obtained and used for the analysis. Figure 5 shows the interaction between the two compounds and A site of 16S RNA. The electrostatic interactions and hydrogen bonds were considered as the major interactions, which were responsible for the ligands binding to the pocket of A site of 16S RNA. For compound **10i**, in addition to the four amino groups of neamine, nucleoside base adenine can form electrostatic interaction with U18 residue of A site of 16S RNA, and for compound **10q**, besides the four amino groups of neamine, the NH_2 on the guanidino group can form electrostatic interaction with A21 residue of A site of 16S RNA and the nucleobase guanine can form hydrogen bond with U23 residue of A site of 16S RNA. Figure 5a and b indicates that the amino acid–ethylenediamine linker could lead the neamine–nucleoside conjugates to the binding pocket of RNA and help improving the binding affinities to the target RNA. The molecular docking study is in agreement with the experimental data.

2.3. Conclusion

Eighteen novel neamine–nucleoside conjugates **10a**–**r** with ethylenediamine–lysine or ethylenediamine–arginine as the linker were synthesized and their potential binding to 16S RNA and TAR RNA was evaluated using SPR (surface plasmon resonance). Compared with neamine, compounds **10i** and **10q** show 6.3 and 4.8 times potential in binding to A site of 16S RNA and eight and six times potential in binding to TAR RNA, respectively. According to the data of SPR, it indicate that amino acid residue and nucleobase exhibit the important contributions for the binding of the designed neamine–nucleosides conjugates to A site of 16S RNA and TAR RNA. The molecular docking study on the interaction between the ligands and A site of 16S RNA is in agreement with the experimental data. The novel type of modification may provide a promising way for the development of neamine derivatives effectively targeting to RNAs.

3. Experimental section

3.1. Synthesis of neamine–nucleosides

*3.1.1. General procedures for the synthesis of neamine–nucleoside conjugates **10a**–**r***

All chemical reagents and solvents were purchased from commercial suppliers. DMF was distilled from P_2O_5 below 40 °C. Silica gel 60H (200–300 mesh) manufactured by Qing-dao Haiyang Chemical Company (China) was used for column chromatography. ^1H and ^{13}C NMR spectra were recorded on Bruker 400 MHz instrument with TMS as an internal standard. HRMS was obtained at MDS SCIEX QSTAR and Bruker DALTONICS APEX IV 70e

instruments, and the data were reported in *m*/*e* (intensity to 100%). UV absorption spectra were recorded on Cary 300 and optical rotations were obtained by Rudolph Research Analytical Autopol III Automatic Polarimeter.

*3.1.2. General procedure for the synthesis of **4a–d***

To a solution of nucleosides **3a–d** (2.0 g) in acetone (120 mL) was added $HClO_4$ (70%, 0.9 mL), the reaction mixture was kept stirring for 1.5 h at room temperature before aqueous ammonia (28%, 1.5 mL) was added. After standing by 3 h, the reaction mixture was filtered and compounds **4a–d** were obtained as white powder.

*3.1.2.1. 2′,3′-O-Isopropylidene-adenosine (**4a**).* Yield: 78% from **3a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (s, 1H, H-8), 8.15 (s, 1H, H-2), 7.34 (s, 2H, –NH_2), 6.12 (d, J=3.0 Hz, H-1′), 5.35 (dd, 1H, J=6.0, 3.0 Hz, H-2′), 5.23 (t, 1H, J=5.5 Hz, –OH), 4.96 (dd, 1H, J=4.8, 2.5 Hz, H-3′), 4.20–4.22 (m, 1H, H-4′), 3.52–3.55 (m, 2H, H-5′), 1.55 (s, 3H, –CH_3), 1.33 (s, 3H, –CH_3).

*3.1.2.2. 2′,3′-O-Isopropylidene-cytidine (**4b**).* Yield: 74% from **3b**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72 (d, 1H, J=7.4 Hz, H-6), 7.27 (d, J=33.0 Hz, 2H, –NH_2), 5.77 (d, J=2.0 Hz, 1H, H-1′), 5.71 (d, 1H, J=7.4 Hz, H-5), 4.99 (t, 1H, J=5.1 Hz, –OH), 4.85 (dd, 1H, J=6.3, 2.1 Hz, H-2′), 4.74 (dd, 1H, J=6.2, 3.8 Hz, H-3′), 4.03 (dd, 1H, J=8.3, 4.3 Hz, H-4′), 3.55–3.59 (m, 2H, H-5′), 1.48 (s, 3H, –CH_3), 1.28 (s, 3H, –CH_3).

*3.1.2.3. 2′,3′-O-Isopropylidene-guanosine (**4c**).* Yield: 79% from **3c**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.66 (br, 1H, H-1), 7.91 (s, 1H, H-8), 6.50 (s, 2H, –NH_2), 5.92 (d, J=3.0 Hz, H-1′), 5.19 (dd, 1H, J=6.5, 3.0 Hz, H-2′), 5.03 (t, 1H, J=5.5 Hz, –OH), 4.97 (dd, 1H, J=6.5, 3.0 Hz, H-3′), 4.10–4.13 (m, 1H, H-4′), 3.51–3.54 (m, 2H, H-5′), 1.51 (s, 3H, –CH_3), 1.32 (s, 3H, –CH_3).

*3.1.2.4. 2′,3′-O-Isopropylidene-inosine (**4d**).* Yield: 75% from **3d**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.42 (s, 1H, H-1), 8.31 (s, 1H, H-2), 8.09 (s, 1H, H-8), 6.10 (d, 1H, J=3.0 Hz, H-1′), 5.26 (dd, 1H, J=6.0, 3.0 Hz, H-2′), 5.11 (t, 1H, J=5.0 Hz, –OH), 4.93 (dd, 1H, J=6.5, 2.5 Hz, H-3′), 4.20–4.24 (m, 1H, H-4′), 3.52–3.55 (m, 2H, H-5′), 1.54 (s, 3H, –CH_3), 1.32 (s, 3H, –CH_3).

*3.1.3. General procedure for the synthesis of **5a–d**[18]*

Compounds **4a–d** (3 mmol), BAIB (6 mmol), and TEMPO (0.6 mmol) were mixed and to this mixture was added 2 mL of a 1:1 CH_3CN/H_2O solution. The reaction mixture was stirred for 4 h at room temperature. The solvent was removed and the residue was washed with diethyl ether and acetone to afford compounds **5a–d** as white foam.

*3.1.3.1. 5′-Carboxylic acid-2′,3′-O-isopropylidene-adenosine (**5a**).* Yield: 82% from **4a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42 (s, 1H, H-8), 8.01 (s, 1H, H-2), 7.25 (s, 2H, –NH_2), 6.28 (s, 1H, H-1′), 5.34–5.38 (m, 2H, H-2′ and 3′), 4.60 (s, 1H, H-4′), 1.52 (s, 3H, –CH_3), 1.34 (s, 3H, –CH_3).

*3.1.3.2. 5′-Carboxylic acid-2′,3′-O-isopropylidene-cytidine (**5b**).* Yield: 77% from **4b**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.51 (br, 1H, –COOH), 7.72 (d, 1H, J=6.0 Hz, H-6), 7.22 (d, 2H, J=26.0 Hz, –NH_2), 5.67 (d, J=7.0 Hz, 1H, H-5), 5.63 (s, 1H, H-1′), 5.52 (dd, 1H, J=6.0, 2.0 Hz, H-3′), 5.06 (d, 1H, J=6.0 Hz, H-2′), 4.47 (d, 1H, J=2.0 Hz, H-4′), 1.45 (s, 3H, –CH_3), 1.29 (s, 3H, –CH_3).

*3.1.3.3. 5′-Carboxylic acid-2′,3′-O-isopropylidene-guanosine (**5c**).* Yield: 79% from **4c**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.80 (s, 1H, H-1), 8.03 (s, 1H, H-8), 6.55 (s, 2H, –NH_2), 6.03 (d, 1H, J=1.0 Hz, H-1′), 5.32 (s, 1H, H-2′), 5.15 (d, 1H, J=5.5 Hz, H-3′), 4.48 (s, 1H, H-4′), 1.51 (s, 3H, –CH_3), 1.36 (s, 3H, –CH_3).

*3.1.3.4. 5′-Carboxylic acid-2′,3′-O-isopropylidene-inosine (**5d**).* Yield: 75% from **4d**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (s, 1H, H-2), 8.01 (s, 1H, H-8), 6.31 (s, 1H, H-1′), 5.45 (d, 1H, J=5.5 Hz, H-2′), 5.40 (d, 1H, J=5.5 Hz, H-3′), 4.70 (s, 1H, H-4′), 1.52 (s, 3H, –CH_3), 1.34 (s, 3H, –CH_3).

*3.1.4. General procedure for the synthesis of **7a** and **7b***

DCC (29 mg, 0.14 mmol), HOBt (19 mg, 0.14 mmol), and Fmoc-Arg(Pbf)-OH or Boc-Lys(Fmoc)-OH (0.14 mmol) were dissolved in anhydrous DMF (1.5 mL). The mixture was stirred in an ice bath for 0.5 h then compound **6** (55 mg, 0.12 mmol) was added. After 6 h, the reaction mixture was filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2/CH_3OH=100:4) to afford a white foam.

*3.1.4.1. epi-5-N[[[$^{\alpha}$N-(tert-Butoxycarbonyl)-$^{\varepsilon}$N-(9-fluorenylmethyloxycarbonyl)]-lysinyl]aminoethyl]-1,3,2′,6′-tetraazido neamine (**7a**).* Yield: 74% from **6**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 7.79 (d, 2H, J=7.5 Hz, 2×Fmoc-H), 7.65 (d, 2H, J=7.4 Hz, 2×Fmoc-H), 7.39 (t, 2H, J=7.4 Hz, 2×Fmoc-H), 7.31 (t, 2H, J=7.4 Hz, 2×Fmoc-H), 5.11 (d, 1H, J=3.5 Hz, H-1′), 4.35 (d, 2H, J=6.8 Hz, Fmoc-CH_2–), 4.20 (t, 1H, J=6.8 Hz, Fmoc-CH–), 3.98–4.02 (m, 2H, H-5′ and Lys-α-CH–), 3.76–3.92 (m, 3H, H-3′, 1 and 3), 3.59–3.62 (dd, 1H, J=10.2, 3.2 Hz, H-4), 3.50–3.54 (dd, 1H, J=13.3, 2.2 Hz, H-6′a), 3.27–3.41 (m, 7H, H-2′, 4′, 5, 6, 6′b and Lys-CH_2-), 2.98–3.07 (m, 2H, Eda-CH_2–), 3.10–3.14 (m, 2H, Eda-CH_2–), 2.18–2.22 (m, 1H, H_{eq}-2), 1.58–1.76 (m, 2H, Lys-CH_2-), 1.48–1.52 (m, 2H, Lys-CH_2–), 1.32–1.48 (m, 2H, Lys-CH_2–), 1.44 (s, 9H, –CH_3×3), 1.13–1.23 (q, 1H, J=12.5 Hz, H_{ax}-2). ^{13}C NMR (100 MHz, CD_3OD): δ 178.00 (–C═O), 158.99 (–C═O), 157.90 (–C═O), 145.39 (2×Fmoc-C), 142.62 (2×Fmoc-C), 128.78 (2×Fmoc-C), 128.16 (2×Fmoc-C), 126.19 (2×Fmoc-C), 120.94 (2×Fmoc-C), 95.62 (C-1′), 80.66 (Boc-C), 78.97 (C-4), 75.79 (C-4′), 73.53 (C-6), 73.13 (C-3′), 72.59 (C-5), 67.64 (Fmoc-CH_2–), 64.91 (C-5′), 60.69 (C-2′), 59.72 (C-1), 59.44 (C-3), 56.50 (Lys-α-C), 52.53 (C-6′), 50.42 (Eda-CH_2– and Fmoc-CH–), 41.29 (Eda-CH_2– and Lys-CH_2–), 33.68 (C-2), 33.09 (Lys-CH_2–), 30.52 (Lys-CH_2–), 28.75 (3×Boc-CH_3), 24.09 (Lys-CH_2–). HRMS calcd for $C_{40}H_{54}N_{16}O_{10}$ ($[M+H]^+$): 919.4282, found: 919.4278. $[\alpha]_D^{20}$ 0.545 (CH_3OH, *c* 0.099).

*3.1.4.2. epi-5-N[[[$^{\alpha}$N-(9-Fluorenylmethyloxycarbonyl)-^{G}N-(2,2,4,6,7-pentamethyl dihydrobenzofuran-5-sulfonyl)]arginyl]aminoethyl]-1,3,2′,6′-tetraazido neamine (**7b**).* Yield: 79% from **6**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 7.78 (d, 2H, J=7.5 Hz, 2×Fmoc-H), 7.66 (t, 2H, J=7.7 Hz, 2×Fmoc-H), 7.38 (t, 2H, J=7.5 Hz, 2×Fmoc-H), 7.30 (t, 2H, J=7.3 Hz, 2×Fmoc-H), 5.12 (d, 1H, J=3.0 Hz, H-1′), 4.37–4.47 (m, 2H, Fmoc-CH_2–), 4.21 (t, 1H, J=6.8 Hz, Fmoc-CH–), 4.06–4.13 (m, 1H, Arg-α-CH–), 3.98–4.01 (m, 1H, H-5′), 3.75–3.94 (3H, H-1, 3 and 3′), 3.58–3.61 (dd, 1H, J=9.2, 2.7 Hz, H-4), 3.50 (dd, 1H, J=11.3, 2.1 Hz, H-6′a), 3.27–3.44 (m, 7H, H-6′b, 2′, 4′, 5, 6, and Arg-CH_2–), 3.15–3.18 (m, 2H, Eda-CH_2–), 2.96–3.08 (m, 2H, Eda-CH_2–), 2.98 (s, 2H, Pbf-CH_2–), 2.59 (s, 3H, Pbf-CH_3), 2.52 (s, 3H, Pbf-CH_3), 2.14–2.17 (m, 1H, H_{eq}-2), 2.07 (s, 3H, Pbf-CH_3), 1.52–1.79 (m, 4H, 2×Arg-CH_2–), 1.42 (s, 6H, 2×Pbf-CH_3), 1.11–1.20 (m, 1H, H_{ax}-2). ^{13}C NMR (100 MHz, CD_3OD): δ 174.81 (–C═O), 159.90 (Pbf-C), 158.46 (–C═O), 158.17 (–C═NH), 145.39 (2×Fmoc-C), 142.63 (2×Fmoc-C), 139.43 (Pbf-C), 134.32 (Pbf-C), 133.55 (Pbf-C), 128.80 (2×Fmoc-C), 128.19 (2×Fmoc-C), 126.22 (2×Fmoc-C), 126.05 (Pbf-C), 120.95 (2×Fmoc-C), 118.47 (Pbf-C), 95.72 (C-1′), 87.65 (Pbf-C), 79.50 (C-4), 75.67 (C-4′), 73.53 (C-6), 73.14 (C-3′), 72.58 (C-5), 67.85 (Fmoc-CH_2–), 64.90 (C-5′), 60.66 (C-2′), 59.69 (C-1), 59.47 (C-3), 56.50 (Arg-α-CH–), 52.52 (C-6′), 50.45 (Eda-CH_2– and Fmoc-CH–), 43.95 (Pbf-CH_2–), 41.30 (Eda-CH_2– and Arg-CH_2–), 33.50 (C-2 and Arg-CH_2–), 28.68 (2×Pbf-CH_3 and Arg-CH_2–), 19.63 (Pbf-CH_3), 18.43 (Pbf-CH_3), 12.52 (Pbf-CH_3). HRMS calcd for $C_{48}H_{62}N_{18}O_{11}S$ ($[M+H]^+$): 1099.4639, found: 1099.4643. $[\alpha]_D^{20}$ 0.446 (H_2O, *c* 0.101).

*3.1.5. epi-5-N[[[$^{\varepsilon}$N-(9-Fluorenylmethyloxycarbonyl)]-lysinyl]aminoethyl]-1,3,2′,6′-tetraazido neamine (**8a**)*

Compound **7a** (50 mg, 0.05 mmol) was dissolved in 20% CF_3COOH in CH_2Cl_2 (2 mL) and kept stirring for about 1.5 h at room temperature then Et_2O (2 mL) was added and the white solid precipitated was purified by column chromatography on silica gel with gradient elution (CH_2Cl_2/CH_3OH=100:5) and the final pure product **8a** was obtained as a white foam (34 mg, yield 76%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.79 (d, 2H, J=7.5 Hz, 2×Fmoc-H), 7.65 (d, 2H, J=7.4 Hz, 2×Fmoc-H), 7.39 (t, 2H, J=7.4 Hz, 2×Fmoc-H), 7.32 (t, 2H, J=7.4 Hz, 2×Fmoc-H), 5.10 (d, 1H, J=3.5 Hz, H-1′), 4.35 (d, 2H, J=6.8 Hz, Fmoc-CH_2–), 4.20 (t, 1H, J=6.8 Hz, Fmoc-CH–), 3.98–4.03 (m, 1H, H-5′), 3.78–3.93 (m, 3H, H-1, 3 and 3′), 3.60 (dd, 1H, J=10.2, 3.2 Hz, H-4), 3.52 (dd, 1H, J=13.3, 2.2 Hz, H-6′a), 3.31–3.44 (m, 8H, H-6′b, 2′, 4, 5, 6, Lys-α-CH– and Lys-CH_2–), 3.11–3.14 (m, 2H, Eda-CH_2–), 2.94–3.06 (m, 2H, Eda-CH_2–), 2.17–2.22 (m, 1H, H_{eq}-2), 1.36–1.45 (m, 2H, Lys-CH_2–), 1.48–1.74 (m, 4H, 2×Lys-CH_2–), 1.13–1.22 (q, 1H, J=12.5 Hz, H_{ax}-2). ^{13}C NMR (100 MHz, CD_3OD): δ 177.74 (–C═O), 158.94 (–C═O), 145.38 (2×Fmoc-C), 142.62 (2×Fmoc-C), 128.78 (2×Fmoc-C), 128.16 (2×Fmoc-C), 126.18 (2×Fmoc-C), 120.94 (2×Fmoc-C), 95.61 (C-1′), 78.94 (C-4), 75.83 (C-4′), 73.55 (C-6), 73.12 (C-3′), 72.59 (C-5), 67.67 (Fmoc-CH_2–), 64.92 (C-5′), 60.78 (C-2′), 59.79 (C-1), 59.37 (C-3), 56.21 (Lys-α-CH–), 52.53 (C-6′), 50.53 (Eda-CH_2– and Fmoc-CH–), 41.15 (Eda-CH_2– and Lys-CH_2–), 36.01 (Lys-CH_2–), 33.67 (C-2), 30.72 (Lys-CH_2–), 23.92 (Lys-CH_2–). HRMS calcd for $C_{35}H_{46}N_{16}O_8$ ($[M+H]^+$): 819.3757, found: 819.3759. $[\alpha]_D^{20}$ 0.707 (CH_3OH, *c* 0.075).

*3.1.6. epi-5-N[[[$^{\alpha}$N-(tert-Butoxycarbonyl)]lysinyl]aminoethyl]-1,3,2′,6′-tetraazido neamine (**8b**)*

Compound **7a** (30 mg, 0.03 mmol) was dissolved in 10% Et_2NH in DMF (1 mL), after stirring for 10 min at room temperature, the resulting mixture was concentrated and the residue was purified by column chromatography on silica gel (CH_2Cl_2/CH_3OH=100:15) to afford a white foam (19 mg, yield 84%). ^{1}H NMR (400 MHz, CD_3OD): δ 5.15 (d, 1H, J=3.5 Hz, H-1′), 3.78–4.03 (m, 4H, H-5′, 1, 3 and 3′), 3.61 (dd, 1H, J=10.2, 3.2 Hz, H-4), 3.52 (dd, 1H, J=13.3, 2.2 Hz, H-6′a), 3.31–3.65 (m, 8H, H-6′b, 2′, 4, 5, 6, Lys-α-CH– and Lys-CH_2–), 2.98–3.08 (m, 2H, Eda-CH_2–), 2.85–2.89 (m, 2H, Eda-CH_2–), 2.18–2.24 (m, 1H, H_{eq}-2), 1.62–1.80 (m, 4H, 2×Lys-CH_2–), 1.46 (s, 9H, 3×Boc-CH_3), 1.29–1.59 (m, 2H, Lys-CH_2–), 1.19 (m, 1H, H_{ax}-2). ^{13}C NMR (100 MHz, CD_3OD): δ 175.06 (–C═O), 157.91 (–C═O), 95.62 (C-1′), 80.80 (Boc-C), 78.98 (C-4), 75.76 (C-4′), 73.56 (C-6), 73.14 (C-3′), 72.59 (C-5), 64.92 (C-5′), 60.69 (C-2′), 59.75 (C-1), 59.46 (C-3), 55.93 (Lys-α-CH–), 52.53 (C-6′), 50.41 (Eda-CH_2–), 41.43 (Eda-CH_2–), 40.79 (Lys-CH_2–), 33.69 (C-2), 32.92 (Lys-CH_2–), 30.75 (Lys-CH_2–), 28.75 (3×Boc-CH_3), 23.95 (Lys-CH_2–). HRMS calcd for $C_{25}H_{44}N_{16}O_8$ ($[M+H]^+$): 697.3601, found: 697.3601. $[\alpha]_D^{20}$ 0.370 (CH_3OH, *c* 0.081).

*3.1.7. epi-5-N[[[^{G}N-(2,2,4,6,7-Pentamethyldihydrobenzofuran-5-sulfonyl)]arginyl]aminoethyl]-1,3,2′,6′-tetraazido neamine (**8c**)*

Compound **7b** (68 mg, 0.06 mmol) was dissolved in 10% Et_2NH in DMF (1 mL), after stirring for 10 min at room temperature, the resulting mixture was concentrated and the residue was purified by column chromatography on silica gel (CH_2Cl_2/CH_3OH=100:5) to afford a white foam (46 mg, yield 85%). ^{1}H NMR (400 MHz, CD_3OD): δ 5.15 (d, 1H, J=3.5 Hz, H-1′), 4.00–4.04 (m, 1H, H-5′), 3.80–3.96 (m, 3H, H-1, 3 and 3′), 3.61 (dd, 1H, J=10.2, 3.2 Hz, H-4), 3.52 (dd, 1H, J=13.3, 2.2 Hz, H-6′a), 3.27–3.46 (m, 8H, H-6′b, 2′, 4′, 5, 6, Arg-CH_2– and Arg-α-CH–), 3.10–3.25 (m, 2H, Eda-CH_2–), 2.96–3.08 (m, 2H, Eda-CH_2–), 3.00 (s, 2H, Pbf-CH_2–), 2.58 (s, 3H, Pbf-CH_3), 2.52 (s, 3H, Pbf-CH_3), 2.17–2.22 (m, 1H, H_{eq}-2), 2.07 (s, 3H, Pbf-CH_3), 1.56–1.72 (m, 4H, 2×Arg-CH_2-), 1.45 (s, 6H, 2×Pbf-CH_3), 1.15 (q, 1H, J=12.5 Hz, H_{ax}-2). ^{13}C NMR (100 MHz, CD_3OD): δ 177.26 (–C═O), 159.89 (Pbf-C), 158.14 (–C═NH), 139.40 (Pbf-C), 134.35 (Pbf-C), 133.53 (Pbf-C), 126.04 (Pbf-C), 118.46 (Pbf-C), 95.67 (C-1′), 87.69 (Pbf-C), 79.03 (C-4), 75.81 (C-4′), 73.55 (C-6), 73.12 (C-3′), 72.58 (C-5), 64.92 (C-5′), 60.76 (C-2′), 59.80 (C-1), 59.42 (C-3), 55.75 (Arg-α-CH–), 52.54 (C-6′), 50.58 (Eda-CH_2–), 43.98 (Pbf-CH_2–), 41.18 (Eda-CH_2– and Arg-CH_2–), 33.66 (C-2), 33.24 (Arg-CH_2–), 28.72 (2×Pbf-CH_3 and Arg-CH_2–), 19.59 (Pbf-CH_3), 18.40 (Pbf-CH_3), 12.51 (Pbf-CH_3). HRMS calcd for $C_{33}H_{52}N_{18}O_9S$ ($[M+H]^+$): 877.3958, found: 877.3955. $[\alpha]_D^{20}$ 0.599 (CH_3OH, *c* 0.089).

*3.1.8. General procedure for the synthesis of **9a**–**r***

DCC (0.13 mmol), HOBt (0.13 mmol), and compounds **2a**, **2b**, **5a**, **5b**, **5c** or **5d** (0.13 mmol) were dissolved in 1.5 mL anhydrous DMF. The mixture was stirred in an ice bath for 0.5 h then compound **8a**, **8b** or **8c** (0.10 mmol) was added. After 6 h, the reaction mixture was filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2/CH_3OH=100:3) to afford a white foam.

*3.1.8.1. Compound **9a**.* Yield: 80% from **8a**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 7.84 (s, 1H, H-6), 7.78 (d, 2H, J=7.6 Hz, 2×Fmoc-H), 7.63 (d, 2H, J=7.4 Hz, 2×Fmoc-H), 7.38 (t, 2H, J=7.4 Hz, 2×Fmoc-H), 7.30 (t, 2H, J=7.4 Hz, 2×Fmoc-H), 6.20 (dd, 1H, J=8.0, 6.1 Hz, H-1′), 5.46 (d, 1H, J=6.1 Hz, H-3′), 5.11 (d, 1H, J=3.6 Hz, H-1‴), 4.51 (d, 1H, J=1.5 Hz, H-4′), 4.34–4.37 (m, 3H, Fmoc-CH_2– and Lys-α-CH–), 4.19 (t, 1H, J=6.8 Hz, Fmoc-CH–), 4.00–4.03 (m, 1H, H-5‴), 3.75–3.94 (m, 3H, H-3‴, 1″ and 3″), 3.59–3.63 (dd, 1H, J=10.2, 3.3 Hz, H-4″), 3.50–3.54 (dd, 1H, J=13.2, 2.2 Hz, H-6‴a), 3.30–3.48 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Lys-CH_2–), 2.98–3.14 (m, 4H, 2×Eda-CH_2–), 2.56–2.60 (m, 1H, H-2′a), 2.33–2.37 (m, 1H, H-2′b), 2.15–2.23 (m, 1H, H_{eq}-2″), 2.10 (s, 3H, –CH_3), 1.87 (s, 3H, –CH_3), 1.72–1.87 (m, 2H, Lys-CH_2–), 1.49–1.54 (m, 2H, Lys-CH_2–), 1.40–1.46 (m, 2H, Lys-CH_2–), 1.14–1.20 (q, 1H, J=12.5 Hz, H_{ax}-2″). HRMS calcd for $C_{47}H_{58}N_{18}O_{14}$ ($[M+H]^+$): 1099.4453, found: 1099.4419. $[\alpha]_D^{20}$ 0.422 (CH_3OH, *c* 0.133). λ_{max}=210 nm, ε=26,356, λ_{max}=265 nm, ε=15,585.

*3.1.8.2. Compound **9b**.* Yield: 77% from **8a**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (d, 1H, J=8.1 Hz, H-6), 7.78 (d, 2H, J=7.5 Hz, 2×Fmoc-H), 7.63 (d, 2H, J=7.5 Hz, 2×Fmoc-H), 7.39 (t, 2H, J=7.5 Hz, 2×Fmoc-H), 7.30 (t, 2H, J=7.5 Hz, 2×Fmoc-H), 5.94 (d, 1H, J=2.6 Hz, H-1′), 5.73 (d, 1H, J=8.0 Hz, H-5), 5.63–5.65 (m, 2H, H-2′ and H-3′), 5.11 (d, 1H, J=3.5 Hz, H-1‴), 4.61 (d, 1H, J=2.6 Hz, H-4′), 4.34–4.38 (m, 3H, Fmoc-CH_2– and Lys-α-CH–), 4.20 (t, 1H, J=7.5 Hz, Fmoc-CH–), 3.99–4.02 (m, 1H, H-5‴), 3.77–3.92 (m, 3H, H-3‴, 1″ and 3″), 3.62 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.53 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.30–3.48 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Lys-CH_2–), 2.99–3.16 (m, 4H, 2×Eda-CH_2–), 2.18–2.23 (m, 1H, H_{eq}-2″), 2.13 (s, 3H, –$COCH_3$), 2.05 (s, 3H, –$COCH_3$), 1.72–1.86 (m, 2H, Lys-CH_2–), 1.47–1.54 (m, 2H, Lys-CH_2–), 1.33–1.46 (m, 2H, Lys-CH_2–), 1.21 (q, 1H, J=12.5 Hz, H_{ax}-2″). HRMS calcd for $C_{48}H_{58}N_{18}O_{16}$ ($[M+H]^+$): 1143.4351, found: 1143.4321. $[\alpha]_D^{20}$ 0.217 (CH_3OH, *c* 0.216). λ_{max}=210 nm, ε=23,203, λ_{max}=263 nm, ε=13,280.

*3.1.8.3. Compound **9c**.* Yield: 73% from **8a**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 8.16 (s, 1H, H-8), 8.14 (s, 1H, H-2), 7.79 (d, 2H, J=7.5 Hz, 2×Fmoc-H), 7.64 (d, 2H, J=7.5 Hz, 2×Fmoc-H), 7.39 (t, 2H, J=7.5 Hz, 2×Fmoc-H), 7.31 (t, 2H, J=7.5 Hz, 2×Fmoc-H), 6.34 (s, 1H, H-1′), 5.67 (dd, 1H, H-2′), 5.46 (d, 1H, H-3′), 5.08 (d, 1H, J=3.5 Hz, H-1‴), 4.75 (d, 1H, J=2.6 Hz, H-4′), 4.37 (d, 2H, J=6.8 Hz, Fmoc-CH_2–), 4.21 (t, 1H, J=6.6 Hz, Fmoc-CH–), 4.00–4.03 (m, 1H, H-5‴), 3.80–3.93 (m, 3H, H-3‴, 1″ and Lys-α-CH–), 3.68–3.73 (m, 1H, H-3″), 3.58 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.53 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.27–3.41 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Lys-CH_2–), 2.86–3.23 (m, 4H, 2×Eda-CH_2–), 2.20 (m, 1H, H_{eq}-2″), 1.58 (s, 3H, –CH_3), 1.39 (s, 3H, –CH_3), 1.11–1.34 (m, 6H, 3×Lys-CH_2–), 1.21 (q, 1H, J=12.5 Hz, H_{ax}-2″). HRMS calcd for $C_{48}H_{59}N_{21}O_{12}$ ($[M+H]^+$): 1122.4725, found: 1122.4681. $[\alpha]_D^{20}$ 0.241 (CH_3OH, *c* 0.207). λ_{max}=210 nm, ε=21,240, λ_{max}=263 nm, ε=12,708.

3.1.8.4. Compound ***9d***. Yield: 75% from **8a**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 7.79 (d, 2H, J=7.5 Hz, 2×Fmoc-H), 7.64 (d, 2H, J=7.5 Hz, 2×Fmoc-H), 7.59 (d, 1H, J=7.4 Hz, H-6), 7.38 (t, 2H, J=7.5 Hz, 2×Fmoc-H), 7.30 (t, 2H, J=7.5 Hz, 2×Fmoc-H), 5.84 (d, 1H, J=7.3 Hz, H-5), 5.60 (s, 1H, H-1′), 5.36 (dd, 1H, J=6.2, 2.0 Hz, H-2′), 5.20 (d, 1H, J=6.3 Hz, H-3′), 5.10 (d, 1H, J=3.5 Hz, H-1‴), 4.59 (d, 1H, J=2.6 Hz, H-4′), 4.34 (d, 2H, J=6.3 Hz, Fmoc-CH_2–), 4.18–4.23 (m, 2H, Fmoc-CH– and Lys-α-CH–), 3.74–4.04 (m, 4H, H-5‴, 3‴, 1″ and 3″), 3.59 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.53 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.27–3.44 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Lys-CH_2–), 2.96–3.14 (m, 4H, 2×Eda-CH_2–), 2.20 (m, 1H, H_{eq}-2″), 1.68–1.73 (m, 2H, Lys-CH_2–), 1.50 (s, 3H, –CH_3), 1.40–1.58 (m, 2H, Lys-CH_2–), 1.32 (s, 3H, –CH_3), 1.17–1.32 (m, 2H, Lys-CH_2–), 1.16 (q, 1H, J=12.5 Hz, H_{ax}-2″). HRMS calcd for $C_{47}H_{59}N_{19}O_{13}$ ([M+H]$^+$): 1098.4613, found: 1098.4602. $[\alpha]_D^{20}$ 0.251 (CH_3OH, *c* 0.187). λ_{max}=210 nm, ε=26,875, λ_{max}=265 nm, ε=13,988.

3.1.8.5. Compound ***9e***. Yield: 70% from **8a**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 7.80 (d, 2H, J=7.5 Hz, 2×Fmoc-H), 7.77 (s, 1H, H-8), 7.66 (d, 2H, J=7.5 Hz, 2×Fmoc-H), 7.40 (t, 2H, J=7.5 Hz, 2×Fmoc-H), 7.32 (t, 2H, J=7.5 Hz, 2×Fmoc-H), 6.21 (s, 1H, H-1′), 5.73 (dd, 1H, J=6.0, 1.8 Hz, H-2′), 5.33 (d, 1H, J=6.0 Hz, H-3′), 5.10 (d, 1H, J=3.5 Hz, H-1‴), 4.74 (d, 1H, J=1.5 Hz, H-4′), 4.36 (d, 2H, J=6.8 Hz, Fmoc-CH_2–), 4.22 (t, 1H, J=6.8 Hz, Fmoc-CH–), 3.70–4.02 (m, 5H, H-5‴, 3‴, 1″, Lys-α-CH- and 3″), 3.58 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.52 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.22–3.44 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Lys-CH_2–), 2.90–3.03 (m, 4H, 2×Eda-CH_2–), 2.18–2.22 (m, 1H, H_{eq}-2″), 1.56 (s, 3H, –CH_3), 1.40 (s, 3H, –CH_3), 1.29–1.42 (m, 6H, 3×Lys-CH_2–), 1.16 (q, 1H, J=12.5 Hz, H_{ax}-2″). HRMS calcd for $C_{48}H_{59}N_{21}O_{13}$ ([M+H]$^+$): 1138.4674, found: 1138.4605. $[\alpha]_D^{20}$ 0.377 (CH_3OH, *c* 0.159). λ_{max}=211 nm, ε=28,154, λ_{max}=262 nm, ε=22,941.

3.1.8.6. Compound ***9f***. Yield: 78% from **8a**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 8.14 (s, 1H, H-2), 8.01 (s, 1H, H-8), 7.79 (d, 2H, J=7.5 Hz, 2×Fmoc-H), 7.65 (d, 2H, J=7.5 Hz, 2×Fmoc-H), 7.38 (t, 2H, J=7.5 Hz, 2×Fmoc-H), 7.29 (t, 2H, J=7.5 Hz, 2×Fmoc-H), 6.35 (s, 1H, H-1′), 5.61 (dd, 1H, J=6.0, 1.7 Hz, H-2′), 5.41 (d, 1H, J=6.0 Hz, H-3′), 5.08 (d, 1H, J=3.5 Hz, H-1‴), 4.77 (d, 1H, J=1.6 Hz, H-4′), 4.35 (d, 2H, J=6.9 Hz, Fmoc-CH_2–), 4.22 (t, 1H, J=6.8 Hz, Fmoc-CH–), 3.73–4.03 (m, 5H, H-5‴, 3‴, 1″, Lys-α-CH- and 3″), 3.58 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.52 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.26–3.44 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Lys-CH_2–), 2.86–3.24 (m, 4H, 2×Eda-CH_2–), 2.18–2.22 (m, 1H, H_{eq}-2″), 1.57 (s, 3H, –CH_3), 1.39 (s, 3H, –CH_3), 1.21 (q, 1H, J=12.5 Hz, H_{ax}-2″), 1.11–1.40 (m, 6H, 3×Lys-CH_2–). HRMS calcd for $C_{48}H_{58}N_{20}O_{13}$ ([M+H]$^+$): 1123.4565, found: 1123.4522. $[\alpha]_D^{20}$ 0.242 (CH_3OH, *c* 0.174). λ_{max}=211 nm, ε=23,650, λ_{max}=255 nm, ε=12,639.

3.1.8.7. Compound ***9g***. Yield: 82% from **8b**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 1H, H-6), 6.30 (dd, 1H, J=8.0, 6.0 Hz, H-1′), 5.41 (d, H, J=5.9 Hz, H-3′), 5.15 (d, 1H, J=3.5 Hz, H-1‴), 4.44 (d, 1H, J=1.5 Hz, H-4′), 3.79–4.04 (m, 5H, H-5‴, 3‴, 1″, 3″ and Lys-α-CH–), 3.62 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.53 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.25–3.47 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Lys-CH_2–), 3.24–3.28 (m, 2H, Eda-CH_2–), 2.97–3.07 (m, 2H, Eda-CH_2–), 2.53–2.58 (m, 1H, H-2′a), 2.36–2.41 (m, 1H, H-2′b), 2.20–2.24 (m, 1H, H_{eq}-2″), 2.12 (s, 3H, –$COCH_3$), 1.91 (s, 3H, –CH_3), 1.57–1.79 (m, 4H, 2×Lys-CH_2–), 1.45 (s, 9H, 3×Boc-CH_3), 1.38–1.45 (m, 2H, Lys-CH_2–), 1.21 (q, 1H, J=12.5 Hz, H_{ax}-2″). HRMS calcd for $C_{37}H_{56}N_{18}O_{14}$ ([M+H]$^+$): 977.4296, found: 977.4315. $[\alpha]_D^{20}$ 0.497 (CH_3OH, *c* 0.187). λ_{max}=208 nm, ε=11,903, λ_{max}=264 nm, ε=7338.

3.1.8.8. Compound ***9h***. Yield: 80% from **8b**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 8.03 (d, 1H, J=8.0 Hz, H-6), 6.00 (d, 1H, J=5.3 Hz, H-1′), 5.76 (d, 1H, J=8.0 Hz, H-5), 5.65 (t, 1H, J=5.6 Hz, H-2′), 5.58 (m, 1H, H-3′), 5.15 (d, 1H, J=3.5 Hz, H-1‴), 4.53 (d, 1H, J=3.7 Hz, H-4′), 3.78–4.04 (m, 5H, H-5‴, 3‴, 1″, 3″ and Lys-α-CH–), 3.62 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.53 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.25–3.47 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Lys-CH_2–), 3.24–3.28 (m, 2H, Eda-CH_2–), 2.97–3.07 (m, 2H, Eda-CH_2–), 2.20–2.24 (m, 1H, H_{eq}-2″), 2.12 (s, 3H, –CH_3), 1.91 (s, 3H, –CH_3), 1.50–1.79 (m, 4H, 2×Lys-CH_2–), 1.45 (s, 9H, 3×Boc-CH_3), 1.33–1.50 (m, 2H, Lys-CH_2–), 1.21 (q, 1H, J=12.5 Hz, H_{ax}-2″). HRMS calcd for $C_{38}H_{56}N_{18}O_{16}$ ([M+H]$^+$): 1021.4194, found: 1021.4189. $[\alpha]_D^{20}$ 0.454 (CH_3OH, *c* 0.183). λ_{max}=207 nm, ε=11,253, λ_{max}=258 nm, ε=6062.

3.1.8.9. Compound ***9i***. Yield: 75% from **8b**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 8.24 (s, 1H, H-8), 8.18 (s, 1H, H-2), 6.36 (d, 1H, J=0.9 Hz, H-1′), 5.63 (dd, 1H, J=6.0, 2.3 Hz, H-2′), 5.52 (d, 1H, J=5.6 Hz, H-3′), 5.15 (d, 1H, J=3.5 Hz, H-1‴), 4.64 (d, 1H, J=1.8 Hz, H-4′), 3.79–4.04 (m, 5H, H-5‴, 3‴, 1″, 3″ and Lys-α-CH–), 3.62 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.53 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.30–3.48 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Lys-CH_2–), 2.96–3.08 (m, 2H, Eda-CH_2–), 2.76–2.87 (m, 2H, Eda-CH_2–), 2.20–2.24 (m, 1H, H_{eq}-2″), 1.59 (s, 3H, –CH_3), 1.47–1.63 (m, 2H, Lys-CH_2–), 1.45 (s, 9H, 3×Boc-CH_3), 1.41 (s, 3H, –CH_3), 1.21 (q, 1H, J=12.5 Hz, H_{ax}-2″), 1.00–1.13 (m, 4H, 2×Lys-CH_2–). HRMS calcd for $C_{38}H_{57}N_{21}O_{12}$ ([M+H]$^+$): 1000.4568, found: 1000.4552. $[\alpha]_D^{20}$ 0.334 (CH_3OH, *c* 0.111). λ_{max}=209 nm, ε=10,295, λ_{max}=260 nm, ε=7107.

3.1.8.10. Compound ***9j***. Yield: 72% from **8b**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 7.65 (d, 1H, J=7.4 Hz, H-6), 5.87 (d, 1H, J=7.4 Hz, H-5), 5.64 (s, 1H, H-1′), 5.26 (d, 1H, H-2′), 5.19 (d, 1H, J=6.0 Hz, H-3′), 5.15 (d, 1H, J=3.5 Hz, H-1‴), 4.49 (d, 1H, J=2.4 Hz, H-4′), 3.81–4.04 (m, 5H, H-5‴, 3‴, 1″, 3″ and Lys-α-CH–), 3.62 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.53 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.30–3.48 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Lys-CH_2–), 2.86–3.30 (m, 4H, 2×Eda-CH_2–), 2.20–2.24 (m, 1H, H_{eq}-2″), 1.60–1.74 (m, 2H, Lys-CH_2–), 1.53 (s, 3H, –CH_3), 1.45 (s, 9H, 3×Boc-CH_3), 1.36 (s, 3H, –CH_3), 1.21 (q, 1H, J=12.5 Hz, H_{ax}-2″), 1.14–1.50 (m, 4H, 2×Lys-CH_2–). HRMS calcd for $C_{37}H_{57}N_{19}O_{13}$ ([M+H]$^+$): 976.4456, found: 976.4451. $[\alpha]_D^{20}$ 0.424 (CH_3OH, *c* 0.203). λ_{max}=209 nm, ε=14,298, λ_{max}=268 nm, ε=4978.

3.1.8.11. Compound ***9k***. Yield: 74% from **8b**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 7.83 (s, 1H, H-8), 6.21 (s, 1H, H-1′), 5.72 (dd, 1H, J=6.0, 1.5 Hz, H-2′), 5.41 (d, 1H, J=6.0 Hz, H-3′), 5.16 (d, 1H, J=3.5 Hz, H-1‴), 4.61 (d, 1H, J=1.6 Hz, H-4′), 3.80–4.05 (m, 5H, H-5‴, 3‴, 1″, 3″ and Lys-α-CH–), 3.62 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.53 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.30–3.48 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Lys-CH_2–), 2.78–3.09 (m, 4H, 2×Eda-CH_2–), 2.22 (m, 1H, H_{eq}-2″), 1.56 (s, 3H, –CH_3), 1.46 (s, 9H, 3×Boc-CH_3), 1.41 (s, 3H, –CH_3), 1.36–1.64 (m, 4H, 2×Lys-CH_2–), 1.21 (q, 1H, J=12.5 Hz, H_{ax}-2″), 1.14–1.24 (m, 2H, Lys-CH_2–). HRMS calcd for $C_{38}H_{57}N_{21}O_{13}$ ([M+H]$^+$): 1016.4518, found: 1016.4517. $[\alpha]_D^{20}$ 0.490 (CH_3OH, *c* 0.165). λ_{max}=206 nm, ε=10,380, λ_{max}=256 nm, ε=8490.

3.1.8.12. Compound ***9l***. Yield: 78% from **8b**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 8.22 (s, 1H, H-2), 8.02 (s, 1H, H-8), 6.39 (s, 1H, H-1′), 5.62 (d, 1H, J=6.0, 1.6 Hz, H-2′), 5.47–5.51 (m, 1H, H-3′), 5.16 (d, 1H, J=3.5 Hz, H-1‴), 4.66 (d, 1H, J=1.8 Hz, H-4′), 3.84–4.04 (m, 5H, H-5‴, 3‴, 1″, 3″ and Lys-α-CH–), 3.62 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.53 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.30–3.48 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Lys-CH_2–), 2.78–3.09 (m, 4H, 2×Eda-CH_2–), 2.20–2.24 (m, 1H, H_{eq}-2″), 1.61 (s, 3H, –CH_3), 1.46 (s, 9H, 3×Boc-CH_3), 1.41 (s, 3H, –CH_3), 1.40–1.64 (m, 4H, 2×Lys-CH_2–), 1.21 (q, 1H, J=12.5 Hz, H_{ax}-2″), 1.12–1.20 (m, 2H, Lys-CH_2–). HRMS calcd for $C_{38}H_{56}N_{20}O_{13}$ ([M+H]$^+$): 1001.4409, found: 1001.4382. $[\alpha]_D^{20}$ 0.413 (CH_3OH, *c* 0.196). λ_{max}=207 nm, ε=11,977, λ_{max}=245 nm, ε=7761.

3.1.8.13. Compound ***9m***. Yield: 78% from **8c**, white foam. ^{1}H NMR (400 MHz, CD_3OD): δ 7.88 (s, 1H, H-6), 6.26 (t, 1H, J=7.0 Hz, H-1′), 5.47 (d, 1H, J=6.0 Hz, H-4′), 5.14 (d, 1H, J=3.5 Hz, H-1‴), 4.52–4.56 (m, 1H, H-3′), 4.44 (dd, 1H, Arg-α-CH–), 3.76–4.07 (m, 4H, H-5‴, H-1″, 3″ and 3‴), 3.61 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.52 (dd, 1H,

J=13.3, 2.2 Hz, H-6‴a), 3.30–3.46 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Arg-CH_2–), 3.14–3.20 (m, 2H, Eda-CH_2–), 2.96–3.10 (m, 2H, Eda-CH_2–), 3.00 (s, 2H, Pbf-CH_2–), 2.63 (m, 1H, H-2′a), 2.58 (s, 3H, –CH_3), 2.52 (s, 3H, –CH_3), 2.37–2.41 (m, 1H, H-2′b), 2.17–2.21 (m, 1H, H_{eq}-2″), 2.13 (s, 3H, –$COCH_3$), 2.07 (s, 3H, –CH_3), 1.88 (s, 3H, –CH_3), 1.65–1.88 (m, 2H, Arg-CH_2–), 1.50–1.65 (m, 2H, Arg-CH_2–), 1.45 (s, 6H, 2×-CH_3), 1.15 (q, 1H, J=12.5 Hz, H_{ax}-2″). HRMS calcd for $C_{45}H_{64}N_{20}O_{15}S$ ($[M+H]^+$): 1157.4654, found: 1157.4641. $[\alpha]_D^{20}$ 0.446 (CH_3OH, c 0.182). λ_{max}=218 nm, ε=35,050, λ_{max}=257 nm, ε=13,363.

*3.1.8.14. Compound **9n***. Yield: 76% from **8c**, white foam. ^1H NMR (400 MHz, CD_3OD): δ 7.96 (d, 1H, J=8.0 Hz, H-6), 5.97 (d, 1H, J=5.0 Hz, H-1′), 5.73 (d, 1H, J=8.0 Hz, H-5), 5.64–5.68 (m, 2H, H-2′ and 3′), 5.15 (d, 1H, J=3.5 Hz, H-1‴), 4.62 (d, 1H, J=1.7 Hz, H-4′), 4.45 (dd, 1H, J=8.5, 5.0 Hz, Arg-α-CH-), 3.76–4.03 (m, 4H, H-5‴, 1″, 3″ and 3‴), 3.61 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.52 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.28–3.46 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Arg-CH_2–), 3.00 (s, 2H, Pbf-CH_2–), 2.95–3.19 (m, 4H, 2×Eda-CH_2–), 2.59 (s, 3H, Pbf-CH_3), 2.52 (s, 3H, Pbf-CH_3), 2.08–2.12 (m, 1H, H_{eq}-2″), 2.15 (s, 3H, –$COCH_3$), 2.08 (s, 3H, –$COCH_3$), 2.07 (s, 3H, Pbf-CH_3), 1.50–1.90 (m, 4H, 2×Arg-CH_2–), 1.46 (s, 6H, 2×Pbf-CH_3), 1.15 (q, 1H, J=12.5 Hz, H_{ax}-2″). HRMS calcd for $C_{46}H_{64}N_{20}O_{17}S$ ($[M+H]^+$): 1201.4552, found: 1201.4576. $[\alpha]_D^{20}$ 0.483 (CH_3OH, c 0.126). λ_{max}=218 nm, ε=46,608, λ_{max}=255 nm, ε=20,341.

*3.1.8.15. Compound **9o***. Yield: 72% from **8c**, white foam. ^1H NMR (400 MHz, CD_3OD): δ 8.26 (s, 1H, H-8), 8.15 (s, 1H, H-2), 6.38 (s, 1H, H-1′), 5.65 (dd, 1H, J=6.0, 1.8 Hz, H-2′), 5.51 (d, J=5.6 Hz, H-3′), 5.12 (d, 1H, J=3.5 Hz, H-1‴), 4.73 (d, 1H, J=1.7 Hz, H-4′), 3.71–4.02 (m, 5H, H-5‴, 1″, 3″, 3‴ and Arg-α-CH–), 3.61 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.52 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.19–3.46 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Arg-CH_2–), 3.00 (s, 2H, Pbf-CH_2–), 2.86–3.06 (m, 4H, 2×Eda-CH_2–), 2.59 (s, 3H, –CH_3), 2.52 (s, 3H, –CH_3), 2.08–2.12 (m, 1H, H_{eq}-2″), 2.09 (s, 3H, –CH_3), 1.60 (s, 3H, –CH_3), 1.45 (s, 6H, 2×-CH_3), 1.41 (s, 3H, –CH_3), 1.16 (q, J=12.5 Hz, H_{ax}-2″), 0.93–1.36 (m, 4H, 2×Arg-CH_2–). HRMS calcd for $C_{46}H_{65}N_{23}O_{13}S$ ($[M+H]^+$): 1180.4926, found: 1180.4910. $[\alpha]_D^{20}$ 0.316 (CH_3OH, c 0.105). λ_{max}=215 nm, ε=45,876, λ_{max}=257 nm, ε=25,712.

*3.1.8.16. Compound **9p***. Yield: 70% from **8c**, white foam. ^1H NMR (400 MHz, CD_3OD): δ 7.64 (d, 1H, J=7.5 Hz, H-6), 5.87 (d, 1H, J=7.4 Hz, H-5), 5.58 (s, 1H, H-1′), 5.22–5.24 (m, 2H, H-2′ and H-3′), 5.12 (d, 1H, J=3.6 Hz, H-1‴), 4.56 (s, 1H, H-4′), 4.32–4.35 (m, 1H, H-5‴), 3.74–4.03 (m, 4H, H-1″, 3″, 3‴ and Arg-α-CH–), 3.61 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.52 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.18–3.46 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Arg-CH_2–), 2.95–3.24 (m, 4H, 2×Eda-CH_2–), 3.00 (s, 2H, Pbf-CH_2–), 2.58 (s, 3H, –CH_3), 2.52 (s, 3H, –CH_3), 2.08–2.12 (m, 1H, H_{eq}-2″), 2.09 (s, 3H, –CH_3), 1.50–1.80 (m, 4H, 2×Arg-CH_2–), 1.53 (s, 3H, –CH_3), 1.45 (s, 6H, 2×-CH_3), 1.35 (s, 3H, –CH_3), 1.16 (q, 1H, J=12.5 Hz, H_{ax}-2″). HRMS calcd for $C_{45}H_{65}N_{21}O_{14}S$ ($[M+H]^+$): 1156.4813, found: 1156.4816. $[\alpha]_D^{20}$ 0.313 (CH_3OH, c 0.163). λ_{max}=218 nm, ε=42,416, λ_{max}=255 nm, ε=15,459.

*3.1.8.17. Compound **9q***. Yield: 71% from **8c**, white foam. ^1H NMR (400 MHz, CD_3OD): δ 7.84 (s, 1H, H-8), 6.24 (s, 1H, H-1′), 5.74 (dd, 2H, J=6.0, 1.8 Hz, H-2′), 5.40 (d, 1H, J=6.0 Hz, H-3′), 5.12 (d, 1H, J=3.6 Hz, H-1‴), 4.73 (d, 1H, J=1.8 Hz, H-4′), 3.75–4.02 (m, 5H, H–H-5‴, 1″, 3″, 3‴ and Arg-α-CH–), 3.59 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.52 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.25–3.46 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Arg-CH_2–), 2.92–3.20 (m, 4H, 2×Eda-CH_2–), 3.01 (s, Pbf-CH_2–), 2.58 (s, 3H, –CH_3), 2.52 (s, 3H, –CH_3), 2.18–2.22 (m, 1H, H_{eq}-2″), 2.09 (s, 3H, –CH_3), 1.57 (s, 3H, –CH_3), 1.45 (s, 6H, 2×-CH_3), 1.41 (s, 3H, –CH_3), 1.11–1.41 (m, 4H, 2×Arg-CH_2–), 1.16 (q, 1H, J=12.5 Hz, H_{ax}-2″). HRMS calcd for $C_{46}H_{65}N_{23}O_{14}S$ ($[M+H]^+$): 1196.4875, found: 1196.4874. $[\alpha]_D^{20}$ 0.344 (CH_3OH, c 0.131). λ_{max}=219 nm, ε=20,832, λ_{max}=256 nm, ε=10,768.

*3.1.8.18. Compound **9r***. Yield: 75% from **8c**, white foam. ^1H NMR (400 MHz, CD_3OD): δ 8.22 (s, 1H, H-2), 8.04 (s, 1H, H-8), 6.40 (s, 1H, H-1′), 5.60 (dd, 1H, J=6.0, 2.4 Hz, H-2′), 5.48 (d, J=6.0 Hz, H-3′), 5.12 (d, 1H, J=3.5 Hz, H-1‴), 4.75 (d, 1H, J=2.5 Hz, H-4′), 3.72–4.03 (m, 5H, H–H-5‴, 1″, 3″, 3‴ and Arg-α-CH–), 3.59 (dd, 1H, J=10.2, 3.2 Hz, H-4″), 3.52 (dd, 1H, J=13.3, 2.2 Hz, H-6‴a), 3.20–3.46 (m, 7H, H-6‴b, 2‴, 4‴, 5″, 6″ and Arg-CH_2–), 3.01 (s, Pbf-CH_2–), 2.92–3.20 (m, 4H, 2×Eda-CH_2–), 2.58 (s, 3H, –CH_3), 2.52 (s, 3H, –CH_3), 2.18–2.22 (m, 1H, H_{eq}-2″), 2.09 (s, 3H, –CH_3), 1.59 (s, 3H, –CH_3), 1.45 (s, 6H, 2×-CH_3), 1.41 (s, 3H, –CH_3), 1.11–1.21 (m, 4H, 2×Arg-CH_2–), 1.16 (q, 1H, J=12.5 Hz, H_{ax}-2″). HRMS calcd for $C_{46}H_{64}N_{22}O_{14}S$ ($[M+H]^+$): 1181.4766, found: 1181.4763. $[\alpha]_D^{20}$ 0.302 (CH_3OH, c 0.155). λ_{max}=218 nm, ε=36,739, λ_{max}=252 nm, ε=17,367.

3.1.9. General procedure for the synthesis of *10a* and *10b*

Compound **9a** or **9b** (0.1 mmol) was dissolved in a solution of 10% Et_2NH in DMF (1 mL), after stirring for 10 min at room temperature, the resulting mixture was concentrated then the residue was added NH_3/CH_3OH (2 mL) and kept stirring for 4 h in an ice bath. The solvent was removed and the residue was dissolved in Py/Et_3N/H_2O (5 mL, 4:3:2) and slowly bubbled by hydrogen sulfide for 1 h at room temperature then the reaction mixture was concentrated in vacuum and the residue was purified by HPLC (1‰ CF_3COOH in H_2O and CH_3OH) to afford compounds **10a** and **10b** as a salt of trifluoroacetic acid.

*3.1.9.1. Compound **10a***. Yield: 58% from **9a**, white foam. ^1H NMR (400 MHz, D_2O): δ 7.63 (s, 1H, H-6), 6.23 (t, 1H, J=6.6 Hz, H-1′), 5.66 (d, 1H, J=3.4 Hz, H-1‴), 4.77–4.81 (m, 1H, H-3′), 4.46 (d, 1H, J=3.4 Hz, H-4′), 4.42–4.45 (m, 1H, H-5‴), 4.30–4.33 (m, 3H, H-3‴, 4″ and 6″), 4.09–4.14 (t, 1H, J=9.3 Hz, Lys-α-CH–), 3.47–4.00 (m, 11H, H-2‴, 4‴, 6‴a, 1″, 6‴b, 3″, 5″ and 2×Eda-CH_2–), 2.99 (t, 2H, J=8.0 Hz, Lys-CH_2–), 2.64–2.75 (m, 2H, H_{eq}-2″ and H-2′a), 2.40–2.47 (m, 1H, H-2′b), 1.92–2.05 (q, 1H, J=12.5 Hz, H_{ax}-2″), 1.92 (s, 3H, –CH_3), 1.67–1.88 (m, 4H, 2×Lys-CH_2–), 1.40–1.44 (m, 2H, Lys-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 175.26 (–C=O), 172.79 (–C=O), 166.48 (C-4), 151.51 (C-2), 139.92 (C-6), 110.92 (C-5), 95.00 (C-1‴), 89.57 (C-1′), 85.19 (C-4′), 73.58 (C-3′ and 4″), 70.28 (C-4‴), 69.56 (C-3‴ and 6″), 68.21 (C-5″), 57.50 (C-2‴), 53.81 (Eda-CH_2–), 52.75 (C-1″ and Lys-α-CH–), 47.50 (C-3″), 46.72 (C-5‴), 39.54 (C-6‴), 39.00 (Eda-CH_2–), 37.69 (Lys-CH_2–), 37.34 (C-2′), 30.09 (Lys-CH_2–), 27.93 (C-2″), 26.23 (Lys-CH_2–), 22.30 (Lys-CH_2–), 11.33 (–CH_3). HRMS calcd for $C_{30}H_{54}N_{10}O_{11}$ ($[M+H]^+$): 731.4046, found: 731.4062. $[\alpha]_D^{28.6}$ 1.063 (H_2O, c 0.073). λ_{max}=265 nm, ε=14,750.

*3.1.9.2. Compound **10b***. Yield: 55% from **9b**, white foam. ^1H NMR (400 MHz, D_2O): δ 7.79 (d, 1H, J=8.0 Hz, H-6), 5.86 (d, 1H, J=8.0 Hz, H-5), 5.73 (d, 1H, J=4.0 Hz, H-1′), 5.53 (d, 1H, J=3.6 Hz, H-1‴), 4.61 (m, 1H, H-2′), 4.47–4.50 (m, 2H, H-3′ and 4′), 3.19–4.29 (m, 16H, H-4″, 5‴, 6″, Lys-α-CH–, 4‴, 5″, 1″, 3″, 2‴, 3‴, 6‴a, 6‴b and 2×Eda-CH_2–), 2.96 (t, 2H, J=8.0 Hz, Lys-CH_2–), 2.55–2.59 (m, 1H, H_{eq}-2″), 1.74–1.86 (m, 3H, H_{ax}-2″ and Lys-CH_2–), 1.62–1.73 (m, 2H, Lys-CH_2–), 1.39–1.43 (m, 2H, Lys-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 177.26 (–C=O), 174.83 (–C=O), 168.91 (C-4), 154.08 (C-2), 147.00 (C-6), 104.78 (C-5), 96.84 (C-1‴), 93.97 (C-1′), 85.38 (C-4′), 75.20 (C-3′), 74.92 (C-2′ and 4″), 72.66 (C-4‴), 72.44 (C-3‴ and 6″), 71.05 (C-5″), 59.33 (C-2‴), 56.67 (Eda-CH_2–), 55.62 (Lys-α-CH–), 52.04 (C-1″), 50.65 (C-3″), 49.55 (C-5‴), 42.33 (C-6‴), 41.77 (Eda-CH_2–), 41.33 (Lys-CH_2–), 32.84 (Lys-CH_2–), 30.96 (C-2″), 28.96 (Lys-CH_2–), 25.01 (Lys-CH_2–). HRMS calcd for $C_{29}H_{52}N_{10}O_{12}$ ($[M+H]^+$): 733.3839, found: 733.3854. $[\alpha]_D^{28.7}$ 1.148 (H_2O, c 0.073). λ_{max}=259 nm, ε=8950.

3.1.10. General procedure for the synthesis of *10c–f*

Compounds **9c–f** (0.1 mmol) were dissolved in a solution of 10% Et_2NH in DMF (2 mL), after stirring for 10 min at room temperature, the mixture was concentrated then the residue was added 90%

CF_3COOH in H_2O (2 mL) and stirred for 3 h in an ice bath. The solvent was removed and the residue was dissolved in $Py/Et_3N/H_2O$ (5 mL, 4:3:2) and slowly bubbled by hydrogen sulfide for 1 h at room temperature, the reaction mixture was concentrated in vacuum and the residue was purified by HPLC (1‰ CF_3COOH in H_2O and CH_3OH) to afford compounds **10c–f** as a salt of trifluoroacetic acid.

*3.1.10.1. Compound **10c**.* Yield: 52% from **9c**, white foam. ^1H NMR (400 MHz, D_2O): δ 8.58 (s, 1H, H-8), 8.46 (s, 1H, H-2), 6.27 (d, 1H, J=5.0 Hz, H-1′), 5.60 (d, 1H, J=3.4 Hz, H-1‴), 4.67–4.72 (3H, H-2′, 3′ and 4′), 4.34–4.38 (m, 2H, H-4″ and 3‴), 4.15–4.25 (m, 2H, H-6″ and 5‴), 4.06 (t, 1H, J=9.0 Hz, Lys-α-CH–), 3.36–3.98 (m, 11H, H-4‴, 5″, 1″, 3″, 2‴, 6‴a, 6‴b and 2×Eda-CH_2–), 2.96 (t, 2H, J=7.6 Hz, Lys-CH_2–), 2.61–2.64 (m, 1H, H_{eq}-2″), 1.89–1.95 (q, 1H, J=12.5 Hz, H_{ax}-2″), 1.66–1.89 (m, 4H, 2×Lys-CH_2–), 1.35–1.40 (m, 2H, Lys-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 176.91 (–C=O), 174.47 (–C=O), 153.59 (C-6), 151.05 (C-2), 148.50 (C-4), 145.70 (C-8), 121.91 (C-5), 95.58 (C-1‴), 91.84 (C-1′), 85.86 (C-4′), 76.03 (C-3′), 75.51 (C-2′), 75.33 (C-4″), 72.82 (C-4‴), 72.52 (C-6″), 71.12 (C-3‴), 65.21 (C-5″), 59.43 (C-2‴), 56.55 (Eda-CH_2–), 55.74 (Lys-α-CH–), 51.94 (C-1″), 50.81 (C-3″), 49.69 (C-5‴), 42.48 (C-6‴), 41.70 (Eda-CH_2–), 41.45 (Lys-CH_2–), 33.32 (Lys-CH_2–), 31.05 (C-2″), 29.02 (Lys-CH_2–), 25.00 (Lys-CH_2–). HRMS calcd for $C_{30}H_{53}N_{13}O_{10}$ ($[M+H]^+$): 756.4111, found: 756.4117. $[\alpha]_D^{28.7}$ 1.123 (H_2O, *c* 0.076). λ_{max}=266 nm, ε=10,800.

*3.1.10.2. Compound **10d**.* Yield: 50% from **9d**, white foam. ^1H NMR (400 MHz, D_2O): δ 8.22 (d, 1H, J=8.0 Hz, H-6), 6.28 (d, 1H, J=8.0 Hz, H-5), 5.86 (d, 1H, J=3.7 Hz, H-1′), 5.67 (d, 1H, J=3.5 Hz, H-1‴), 4.55–4.58 (m, 2H, H-2′ and 3′), 4.33–4.49 (m, 5H, H-4′, 3‴, 5‴, 6″ and 4″), 4.14 (t, 1H, J=9.5 Hz, Lys-α-CH–), 3.35–4.06 (m, 11H, H-4‴, 5″, 1″, 3″, 2‴, 6‴a, 6‴b and 2×Eda-CH_2–), 3.03 (t, 2H, J=7.5 Hz, Lys-CH_2–), 2.64–2.68 (m, 1H, H_{eq}-2″), 2.07 (q, 1H, J=12.5 Hz, H_{ax}-2″), 1.83–1.93 (m, 2H, Lys-CH_2–), 1.69–1.81 (m, 2H, Lys-CH_2–), 1.45–1.53 (m, 2H, Lys-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 177.32 (–C=O), 174.42 (–C=O), 162.32 (C-4), 151.29 (C-2), 148.83 (C-6), 97.65 (C-5), 96.67 (C-1‴), 91.00 (C-1′), 85.13 (C-4′), 75.36 (C-3′), 75.11 (C-2′), 75.01 (C-4″), 72.70 (C-4‴), 72.28 (C-6″), 71.12 (C-3‴), 65.26 (C-5″), 59.68 (C-2‴), 56.57 (Eda-CH_2–), 55.70 (Lys-α-CH–), 52.35 (C-1″), 50.81 (C-3″), 49.98 (C-5‴), 42.44 (C-6‴), 41.88 (Eda-CH_2–), 41.45 (Lys-CH_2–), 33.06 (Lys-CH_2–), 30.97 (C-2″), 29.00 (Lys-CH_2–), 24.97 (Lys-CH_2–). HRMS calcd for $C_{29}H_{53}N_{11}O_{11}$ ($[M+H]^+$): 732.3999, found: 732.3998. $[\alpha]_D^{28.8}$ 1.226 (H_2O, *c* 0.073). λ_{max}=267 nm, ε=13,200.

*3.1.10.3. Compound **10e**.* Yield: 48% from **9e**, white foam. ^1H NMR (400 MHz, D_2O): δ 8.34 (s, 1H, H-8), 6.12 (d, 1H, J=3.0 Hz, H-1′), 5.60 (d, 1H, J=3.3 Hz, H-1‴), 4.94 (t, 1H, J=5.2 Hz, H-2′), 4.86 (m, 1H, H-3′), 4.62 (d, 1H, J=1.3 Hz, H-4′), 4.35 (m, 1H, H-3‴), 4.18–4.36 (m, 3H, H-4″, 5‴ and 6″), 4.07 (t, 1H, J=9.8 Hz, Lys-α-CH–), 3.34–3.99 (m, 11H, H-4‴, 5″, 1″, 3″, 2‴, 6‴a, 6‴b and 2×Eda-CH_2–), 2.90 (t, 2H, J=7.8 Hz, Lys-CH_2–), 2.62 (m, 1H, H_{eq}-2″), 1.91 (q, 1H, J=12.5 Hz, H_{ax}-2″), 1.73–1.76 (m, 2H, Lys-CH_2–), 1.57–1.65 (m, 2H, Lys-CH_2–), 1.16–1.29 (m, 2H, Lys-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 177.94 (–C=O), 175.10 (–C=O), 159.98 (C-6), 157.06 (C-2), 153.35 (C-4), 140.27 (C-8), 115.77 (C-5), 92.79 (C-1‴ and 1′), 85.49 (C-4′), 76.00 (C-3′), 75.50 (C-2′), 73.88 (C-4″), 73.09 (C-4‴), 72.33 (C-6″), 70.91 (C-3‴), 70.59 (C-5″), 60.38 (C-2‴), 56.69 (Eda-CH_2–), 55.43 (Lys-α-CH–), 53.34 (C-1″), 50.59 (C-3″), 49.27 (C-5‴), 42.23 (C-6‴), 41.66 (Eda-CH_2–), 40.14 (Lys-CH_2–), 32.79 (Lys-CH_2–), 30.64 (C-2″), 28.99 (Lys-CH_2–), 24.98 (Lys-CH_2–). HRMS calcd for $C_{30}H_{53}N_{13}O_{11}$ ($[M+H]^+$): 772.4060, found: 772.4045. $[\alpha]_D^{29.0}$ 4.254 (H_2O, *c* 0.015). λ_{max}=263 nm, ε=62,250.

*3.1.10.4. Compound **10f**.* Yield: 53% from **9f**, white foam. ^1H NMR (400 MHz, D_2O): δ 8.39 (s, 1H, H-2), 8.21 (s, 1H, H-8), 6.21 (d, 1H, J=4.0 Hz, H-1′), 5.56 (d, 1H, J=4.0 Hz, H-1‴), 4.78–4.83 (m, 2H, H-2′ and 3′), 4.62 (d, 1H, J=4.4 Hz, H-4′), 4.23–4.37 (m, 4H, H-3‴, 5‴, 6″ and 4″), 4.00 (t, 1H, J=8.8 Hz, Lys-α-CH–), 3.32–3.95 (m, 11H, H-4‴, 5″, 1″, 3″, 2‴, 6‴a, 6‴b and 2×Eda-CH_2–), 2.89 (t, 2H, J=8.0 Hz, Lys-CH_2–), 2.58–2.63 (m, 1H, H_{eq}-2″), 1.88 (q, 1H, J=12.5 Hz, H_{ax}-2″), 1.52–1.79 (m, 4H, 2×Lys-CH_2–), 1.19–1.26 (m, 2H, Lys-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 177.91 (C=O), 174.90 (C=O), 160.99 (C-6), 151.21 (C-4), 149.08 (C-2), 143.24 (C-8), 126.59 (C-5), 94.61 (C-1‴), 92.07 (C-1′), 85.82 (C-4′), 78.27 (C-3′), 76.03 (C-2′), 75.69 (C-4″), 73.33 (C-4‴), 72.35 (C-6″), 70.98 (C-3‴), 70.52 (C-5″), 60.65 (C-2‴), 56.56 (Eda-CH_2–), 55.51 (Lys-α-CH–), 53.42 (C-1″), 50.83 (C-3″), 49.51 (C-5‴), 42.31 (C-6‴), 41.82 (Eda-CH_2–), 40.11 (Lys-CH_2–), 32.97 (Lys-CH_2–), 30.70 (C-2″), 29.01 (Lys-CH_2–), 25.07 (Lys-CH_2–). HRMS calcd for $C_{30}H_{52}N_{12}O_{11}$ ($[M+H]^+$): 757.3051, found: 757.3970. $[\alpha]_D^{28.9}$ 1.058 (H_2O, *c* 0.076). λ_{max}=251 nm, ε=13,150.

*3.1.11. General procedure for the synthesis of **10g** and **10h***

Compound **9g** or **9h** (0.1 mmol) was dissolved in 20% CF_3COOH in CH_2Cl_2 (2 mL), after stirring for 1.5 h at room temperature, Et_2O (2 mL) was added and the white solid precipitated was added NH_3/CH_3OH (2 mL) and stirred for 4 h in an ice bath. The solvent was removed and the residue was dissolved in $Py/Et_3N/H_2O$ (5 mL, 4:3:2) and slowly bubbled by hydrogen sulfide for 1 h at room temperature, the reaction mixture was concentrated in vacuum and the residue was purified by HPLC (1‰ CF_3COOH in H_2O and CH_3OH) to afford compounds **10g** and **10h** as a salt of trifluoroacetic acid.

*3.1.11.1. Compound **10g**.* Yield: 55% from **9g**, white foam. ^1H NMR (400 MHz, D_2O): δ 7.67 (s, 1H, H-6), 6.25 (t, 1H, J=6.8 Hz, H-1′), 5.58 (d, 1H, J=3.6 Hz, H-1‴), 4.64 (m, 1H, H-3′), 4.38 (d, 1H, J=3.0 Hz, H-4′), 3.21–4.31 (m, 18H, H-5‴, H-3‴, 4″, 6″, Lys-α-CH–, 2‴, 4‴, 6‴a, 1″, 6‴b, 3″, 5″, Lys-CH_2– and 2×Eda-CH_2–), 2.57–2.60 (m, 1H, H_{eq}-2″), 2.45–2.52 (m, 1H, H-2′a), 2.29–2.35 (m, 1H, H-2′b), 1.85 (s, 3H, –CH_3), 1.79–1.92 (m, 3H, H_{ax}-2″ and Lys-CH_2–), 1.47–1.54 (m, 2H, Lys-CH_2–), 1.32–1.38 (m, 2H, Lys-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 174.50 (–C=O), 173.82 (–C=O), 169.13 (C-4), 154.39 (C-2), 141.48 (C-6), 113.95 (C-5), 94.59 (C-1‴), 90.32 (C-1′), 87.76 (C-4′), 76.35 (C-3′), 74.09 (C-4″), 73.22 (C-4‴), 72.42 (C-6″), 70.75 (C-3‴), 70.44 (C-5″), 61.05 (C-2‴), 55.68 (Eda-CH_2–), 55.45 (C-1″), 53.10 (Lys-α-CH–), 50.81 (C-3″), 49.43 (C-5‴), 42.27 (C-6‴), 41.38 (Eda-CH_2–), 41.29 (C-2′), 39.88 (Lys-CH_2–), 39.78 (Lys-CH_2–), 33.06 (C-2″), 30.61 (Lys-CH_2–), 24.25 (Lys-CH_2–), 14.20 (–CH_3). HRMS calcd for $C_{30}H_{54}N_{10}O_{11}$ ($[M+H]^+$): 730.3974, found: 730.4062. $[\alpha]_D^{28.3}$ 1.227 (H_2O, *c* 0.073). λ_{max}=264 nm, ε=18,350.

*3.1.11.2. Compound **10h**.* Yield: 54% from **9h**, white foam. ^1H NMR (400 MHz, D_2O): δ 7.92 (d, 1H, J=8.0 Hz, H-6), 5.86 (d, 1H, J=8.0 Hz, H-5), 5.83 (d, 1H, J=4.4 Hz, H-1′), 5.58 (d, 1H, J=3.5 Hz, H-1‴), 4.53 (t, 1H, J=5.0 Hz, H-2′), 4.41 (d, 1H, J=4.8 Hz, H-3′), 4.38 (d, 1H, J=5.2 Hz, H-4′), 3.17–4.36 (m, 18H, H-5‴, H-3‴, 4″, 6″, Lys-α-CH–, 2‴, 4‴, 6‴a, 1″, 6‴b, 3″, 5″, Lys-CH_2– and 2×Eda-CH_2–), 2.56–2.62 (m, 1H, H_{eq}-2″), 1.83–1.89 (m, 3H, H_{ax}-2″ and Lys-CH_2–), 1.51–1.58 (m, 2H, Lys-CH_2–), 1.32–1.40 (m, 2H, Lys-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 173.93 (–C=O), 173.82 (–C=O), 168.85 (C-4), 154.27 (C-2), 145.85 (C-6), 105.00 (C-5), 94.37 (C-1‴ and 1′), 85.24 (C-4′), 75.16 (C-3′), 75.07 (C-2′), 74.25 (C-4″), 73.22 (C-4‴), 72.39 (C-6″ and 3‴), 70.76 (C-5″), 61.03 (C-2‴), 55.69 (Eda-CH_2–), 55.44 (Lys-α-CH–), 52.94 (C-1″), 50.83 (C-3″), 49.33 (C-5‴), 42.25 (C-6‴), 41.31 (Eda-CH_2–), 39.83 (Lys-CH_2–), 33.05 (Lys-CH_2–), 30.53 (C-2″), 24.43 (Lys-CH_2–), 24.20 (Lys-CH_2–). HRMS calcd for $C_{29}H_{52}N_{10}O_{12}$ ($[M+H]^+$): 733.3839, found: 733.3834. $[\alpha]_D^{28.4}$ 1.279 (H_2O, *c* 0.073). λ_{max}=262 nm, ε=14,050.

*3.1.12. General procedure for the synthesis of **10i–l***

Compounds **9i–l** were added a solution of 90% CF_3COOH in H_2O (2 mL), and stirred for 3 h in an ice bath. The solvent was removed

and the residue was dissolved in Py/Et_3N/H_2O (5 mL, 4:3:2) and slowly bubbled by hydrogen sulfide for 1 h at room temperature, the reaction mixture was concentrated in vacuum and the residue was purified by HPLC (1‰ CF_3COOH in H_2O and CH_3OH) to afford compounds **10i–l** as a salt of trifluoroacetic acid.

*3.1.12.1. Compound **10i**.* Yield: 50% from **9i**, white foam. ^1H NMR (400 MHz, D_2O): δ 8.57 (s, 1H, H-8), 8.43 (s, 1H, H-2), 6.21 (d, 1H, J=5.6 Hz, H-1′), 5.57 (d, 1H, J=3.6 Hz, H-1‴), 4.57–4.59 (m, 2H, H-2′ and 3′), 3.14–4.34 (m, 19H, H-4′, 5‴, H-3‴, 4″, 6″, Lys-α-CH–, 2‴, 4‴, 6‴a, 1″, 6‴b, 3″, 5″, Lys-CH_2– and 2×Eda-CH_2–), 2.56–2.61 (m, 1H, H_{eq}-2″), 1.81–1.93 (m, 3H, H_{ax}-2″ and Lys-CH_2–), 1.50–1.57 (m, 2H, Lys-CH_2–), 1.32–1.40 (m, 2H, Lys-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 173.74 (–C=O), 173.65 (–C=O), 152.79 (C-6), 150.93 (C-2), 147.29 (C-4), 145.97 (C-8), 121.81 (C-5), 94.42 (C-1‴), 91.43 (C-1′), 86.13 (C-4′), 75.85 (C-3′), 75.50 (C-2′), 74.37 (C-4″), 73.07 (C-4‴), 72.49 (C-6″), 70.80 (C-3‴), 65.18 (C-5″), 60.78 (C-2‴), 55.72 (Eda-CH_2–), 55.49 (Lys-α-CH–), 52.82 (C-1″), 50.79 (C-3″), 49.46 (C-5‴), 42.30 (C-6‴), 41.34 (Eda-CH_2–), 40.18 (Lys-CH_2–), 33.05 (Lys-CH_2–), 30.65 (C-2″ and Lys-CH_2–), 24.26 (Lys-CH_2–). HRMS calcd for $C_{30}H_{53}N_{13}O_{10}$ ($[M+H]^+$): 756.4111, found: 756.4130. $[\alpha]_D^{28.5}$ 1.219 (H_2O, *c* 0.076). λ_{max}=260 nm, ε=19,200.

*3.1.12.2. Compound **10j**.* Yield: 52% from **9j**, white foam. ^1H NMR (400 MHz, D_2O): δ 8.28 (d, 1H, J=8.0 Hz, H-6), 6.18 (d, 1H, J=3.8 Hz, H-1′), 5.81 (d, 1H, J=8.0 Hz, H-5), 5.56 (d, 1H, J=3.5 Hz, H-1‴), 4.37–4.41 (m, 3H, H-2′, 3′ and 4′), 3.08–4.30 (m, 18H, H-5‴, H-3‴, 4″, 6″, Lys-α-CH–, 2‴, 4‴, 6‴a, 1″, 6‴b, 3″, 5″, Lys-CH_2– and 2×Eda-CH_2–), 2.56–2.64 (m, 1H, H_{eq}-2″), 1.77–1.93 (m, 3H, H_{ax}-2″ and Lys-CH_2–), 1.47–1.52 (m, 2H, Lys-CH_2–), 1.31–1.37 (m, 2H, Lys-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 174.03 (–C=O), 173.65 (–C=O), 161.83 (C-4), 150.87 (C-2), 147.93 (C-6), 97.72 (C-5), 94.68 (C-1‴ and 1′), 85.13 (C-4′), 75.73 (C-3′), 75.04 (C-2′), 73.37 (C-4″), 72.34 (C-4‴), 70.67 (C-3‴ and 6″), 69.82 (C-5″), 61.38 (C-2‴), 55.66 (Eda-CH_2–), 55.39 (Lys-α-CH–), 53.46 (C-1″), 50.78 (C-3″), 49.28 (C-5‴), 42.24 (C-6‴), 41.41 (Eda-CH_2–), 39.30 (Lys-CH_2–), 37.21 (Lys-CH_2–), 33.03 (C-2″), 30.43 (Lys-CH_2–), 24.25 (Lys-CH_2–). HRMS calcd for $C_{29}H_{54}N_{11}O_{11}$ ($[M+H]^+$): 732.4004, found: 732.3984. $[\alpha]_D^{28.5}$ 1.248 (H_2O, *c* 0.073). λ_{max}=265 nm, ε=25,900.

*3.1.12.3. Compound **10k**.* Yield: 48% from **9k**, white foam. ^1H NMR (400 MHz, D_2O): δ 8.92 (s, 1H, H-8), 6.11 (d, 1H, J=4.0 Hz, H-1′), 5.61 (d, 1H, J=3.4 Hz, H-1‴), 4.63 (t, 1H, J=5.0 Hz, H-2′), 4.56 (d, 1H, J=6.0 Hz, H-4′), 3.00–4.16 (m, 19H, H-3′, 5‴, H-3‴, 4″, 6″, Lys-α-CH–, 2‴, 4‴, 6‴a, 1″, 6‴b, 3″, 5″, Lys-CH_2– and 2×Eda-CH_2–), 2.59–2.64 (m, 1H, H_{eq}-2″), 1.82–1.95 (m, 3H, H_{ax}-2″ and Lys-CH_2–), 1.46–1.54 (m, 2H, Lys-CH_2–), 1.24–1.40 (m, 2H, Lys-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 173.86 (2×-C=O), 158.80 (C-6), 157.69 (C-2), 152.84 (C-4), 139.59 (C-8), 114.70 (C-5), 94.62 (C-1‴), 92.63 (C-1′), 85.95 (C-4′), 75.92 (C-3′), 75.42 (C-2′), 74.72 (C-4″), 73.29 (C-4‴), 72.40 (C-6″), 70.74 (C-3‴), 65.15 (C-5″), 61.20 (C-2‴), 55.69 (Eda-CH_2–), 55.44 (Lys-α-CH–), 53.11 (C-1″), 50.84 (C-3″), 49.43 (C-5‴), 49.34 (C-6‴), 42.27 (Eda-CH_2–), 41.42 (Lys-CH_2–), 39.64 (Lys-CH_2–), 33.08 (C-2″), 30.56 (Lys-CH_2–), 24.28 (Lys-CH_2–). HRMS calcd for $C_{30}H_{53}N_{13}O_{11}$ ($[M+H]^+$): 772.4021, found: 772.4038. $[\alpha]_D^{28.8}$ 1.089 (H_2O, *c* 0.077). λ_{max}=257 nm, ε=16,500.

*3.1.12.4. Compound **10l**.* Yield: 54% from **9l**, white foam. ^1H NMR (400 MHz, D_2O): δ 8.50 (s, 1H, H-2), 8.23 (s, 1H, H-8), 6.18 (d, 1H, J=5.4 Hz, H-1′), 5.59 (d, 1H, J=3.6 Hz, H-1‴), 4.78 (m, 1H, H-2′), 4.57–4.58 (m, 2H, H-3′ and 4′), 3.13–4.39 (m, 18H, H-5‴, H-3‴, 4″, 6″, Lys-α-CH–, 2‴, 4‴, 6‴a, 1″, 6‴b, 3″, 5″, Lys-CH_2– and 2×Eda-CH_2–), 2.57–2.62 (m, 1H, H_{eq}-2″), 1.80–1.93 (m, 3H, H_{ax}-2″ and Lys-CH_2–), 1.44–1.49 (m, 2H, Lys-CH_2–), 1.26–1.34 (m, 2H, Lys-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 173.97 (–C=O), 173.83 (–C=O), 160.75 (C-6), 151.17 (C-4), 149.31 (C-2), 143.12 (C-8), 126.11 (C-5), 94.89 (C-1‴), 91.65 (C-1′), 86.30 (C-4′), 75.81 (C-3′), 75.67 (C-2′), 74.45 (C-4″), 74.15 (C-4‴), 73.35 (C-6″), 72.45 (C-3‴), 70.83 (C-5″), 61.11 (C-2‴), 55.75 (Eda-CH_2–), 55.51 (Lys-α-CH–), 53.03 (C-1″), 50.94 (C-3″), 49.53 (C-5‴), 42.33 (C-6‴), 41.32 (Eda-CH_2–), 39.88 (Lys-CH_2–), 33.12 (Lys-CH_2–), 30.72 (C-2″), 28.33 (Lys-CH_2–), 24.31 (Lys-CH_2–). HRMS calcd for $C_{30}H_{52}N_{12}O_{11}$ ($[M+H]^+$): 757.3951, found: 757.3981. $[\alpha]_D^{28.8}$ 1.206 (H_2O, *c* 0.076). λ_{max}=250 nm, ε=10,500.

*3.1.13. General procedure for the synthesis of **10m** and **10n***

Compound **9m** or **9n** (0.1 mmol) was dissolved in CF_3COOH/$PhSCH_3$/H_2O (2 mL, 94:3:3), after stirring for 1 h, the resulting mixture was concentrated and the residue was added NH_3/CH_3OH (2 mL) and kept stirring for 4 h in an ice bath. The solvent was removed and the residue was dissolved in Py/Et_3N/H_2O (5 mL, 4:3:2) and slowly bubbled by hydrogen sulfide for 1 h at room temperature, the reaction mixture was concentrated in vacuum and the residue was purified by HPLC (1‰ CF_3COOH in H_2O and CH_3OH) to afford compounds **10m** and **10n** as a salt of trifluoroacetic acid.

*3.1.13.1. Compound **10m**.* Yield: 56% from **9m**, white foam. ^1H NMR (400 MHz, D_2O): δ 7.53 (s, 1H, H-6), 6.14 (t, 1H, J=6.7 Hz, H-1′), 5.56 (d, 1H, J=3.3 Hz, H-1‴), 4.70–4.80 (m, 1H, H-3′), 4.39 (d, 1H, J=3.6 Hz, H-4′), 3.14–4.39 (m, 18H, H-5‴, H-3‴, 4″, 6″, Arg-α-CH–, 2‴, 4‴, 6‴a, 1″, 6‴b, 3″, 5″, Arg-CH_2– and 2×Eda-CH_2–), 2.59–2.63 (m, 2H, H-2′a and H_{eq}-2″), 2.32–2.40 (m, 1H, H-2′b), 1.84 (s, 3H, –CH_3), 1.83–1.95 (m, 1H, H_{ax}-2″), 1.65–1.85 (m, 2H, Arg-CH_2–), 1.50–1.60 (m, 2H, Arg-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 178.13 (–C=O), 175.49 (–C=O), 169.13 (C-4), 159.36 (–C=NH), 154.25 (C-2), 142.48 (C-6), 113.76 (C-5), 94.42 (C-1‴), 92.24 (C-1′), 87.93 (C-4′), 76.26 (C-3′ and 4″), 73.33 (C-4‴), 72.24 (C-6″), 70.92 (C-3‴), 69.99 (C-5″), 60.72 (C-2‴), 56.28 (Eda-CH_2–), 55.42 (C-1″), 53.68 (Arg-α-CH–), 50.71 (C-3″), 49.38 (C-5‴), 43.12 (C-6‴), 42.23 (Eda-CH_2–), 40.04 (Arg-CH_2–), 39.79 (C-2′), 30.50 (C-2″ and Arg-CH_2–), 27.40 (Arg-CH_2–), 14.05 (–CH_3). HRMS calcd for $C_{30}H_{54}N_{12}O_{11}$ ($[M+H]^+$): 759.4108, found: 759.4114. $[\alpha]_D^{27.6}$ 0.443 (H_2O, *c* 0.076). λ_{max}=265 nm, ε=10,600.

*3.1.13.2. Compound **10n**.* Yield: 54% from **9n**, white foam. ^1H NMR (400 MHz, D_2O): δ 7.76 (d, 1H, J=8.0 Hz, H-6), 5.85 (d, 1H, J=8.0 Hz, H-5), 5.73 (d, 1H, J=4.4 Hz, H-1′), 5.56 (d, 1H, J=3.6 Hz, H-1‴), 4.58 (t, 1H, J=4.6 Hz, H-2′), 4.48–4.52 (m, 2H, H-3′ and 4′), 3.15–4.32 (m, 18H, H-5‴, H-3‴, 4″, 6″, Arg-α-CH–, 2‴, 4‴, 6‴a, 1″, 6‴b, 3″, 5″, Arg-CH_2– and 2×Eda-CH_2–), 2.57–2.61 (m, 1H, H_{eq}-2″), 1.71–1.90 (m, 3H, Arg-CH_2– and H_{ax}-2″), 1.57–1.66 (m, 2H, Arg-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 177.66 (C=O), 174.91 (C=O), 168.91 (C-4), 159.46 (–C=NH), 154.19 (C-2), 147.00 (C-6), 104.96 (C-5), 96.81 (C-1‴), 94.41 (C-1′), 85.56 (C-4′), 75.24 (C-3′), 74.93 (C-2′), 74.45 (C-4″), 73.05 (C-4‴), 72.51 (C-6″ and 3‴), 71.06 (C-5″), 60.18 (C-2‴), 56.45 (Eda-CH_2–), 55.60 (Arg-α-CH–), 53.04 (C-1″), 50.79 (C-3″), 49.58 (C-5‴), 43.20 (C-6‴), 42.37 (Eda-CH_2–), 40.72 (Arg-CH_2–), 30.82 (C-2″), 30.57 (Arg-CH_2–), 27.47 (Arg-CH_2–). HRMS calcd for $C_{29}H_{52}N_{12}O_{12}$ ($[M+H]^+$): 761.3900, found: 761.3916. $[\alpha]_D^{27.9}$ 1.211 (H_2O, *c* 0.076). λ_{max}=261 nm, ε=13,300.

*3.1.14. General procedure for the synthesis of **10o–r***

Compounds **9o–r** (0.1 mmol) were dissolved in CF_3COOH/$PhSCH_3$/H_2O (2 mL, 94:3:3), after stirring for 1 h, the resulting mixture was concentrated and the residue was dissolved in Py/Et_3N/H_2O (5 mL, 4:3:2) and slowly bubbled by hydrogen sulfide for 1 h at room temperature, the reaction mixture was concentrated in vacuum and the residue was purified by HPLC (1‰ CF_3COOH in H_2O and CH_3OH) to afford compounds **10o–r** as a salt of trifluoroacetic acid.

*3.1.14.1. Compound **10o**.* Yield: 51% from **9o**, white foam. ^1H NMR (400 MHz, D_2O): δ 8.52 (s, 1H, H-8), 8.41 (s, 1H, H-2), 6.22 (d, 1H,

J=5.2 Hz, H-1′), 5.56 (d, 1H, J=3.6 Hz, H-1‴), 4.64–4.79 (m, 3H, H-2′, 3′ and 4′), 3.08–4.39 (m, 18H, H-5‴, H-3‴, 4″, 6″, Arg-α-CH–, 2‴, 4‴, 6‴a, 1″, 6‴b, 3″, 5″, Arg-CH_2– and 2×Eda-CH_2–), 2.59–2.63 (m, 1H, H_{eq}-2″), 1.84–1.93 (m, 1H, H_{ax}-2″), 1.64–1.81 (m, 2H, Arg-CH_2–), 1.45–1.55 (m, 2H, Arg-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 177.57 (–C═O), 174.44 (–C═O), 159.35 (–C═NH), 152.72 (C-6), 150.80 (C-2), 147.21 (C-4), 146.09 (C-8), 121.85 (C-5), 96.00 (C-1‴), 91.96 (C-1′), 85.70 (C-4′), 76.07 (C-3′), 75.29 (C-2′), 73.28 (C-4″), 72.29 (C-4‴), 70.88 (C-6″ and 3‴), 70.28 (C-5″), 60.70 (C-2‴), 56.17 (Eda-CH_2–), 55.43 (Arg-α-CH–), 53.42 (C-1″), 50.72 (C-3″), 49.40 (C-5‴), 43.01 (C-6‴), 42.24 (Eda-CH_2–), 39.81 (Arg-CH_2–), 30.63 (C-2″ and Arg-CH_2–), 27.24 (Arg-CH_2–). HRMS calcd for $C_{30}H_{53}N_{15}O_{10}$ ([M+H]$^+$): 784.4173, found: 784.4174. $[\alpha]_D^{28.1}$ 1.254 (H_2O, c 0.052). λ_{max}=261 nm, ε=16,392.

*3.1.14.2. Compound **10p**.* Yield: 52% from **9p**, white foam. ^{1}H NMR (400 MHz, D_2O): δ 8.11 (d, 1H, J=8.0 Hz, H-6), 6.20 (d, 1H, J=8.0 Hz, H-5), 5.76 (d, 1H, J=3.5 Hz, H-1′), 5.57 (d, 1H, J=2.8 Hz, H-1‴), 4.50–4.53 (m, 2H, H-2′ and 3′), 4.42 (t, 1H, J=5.6 Hz, H-4′), 3.14–4.37 (m, 18H, H-5‴, H-3‴, 4″, 6″, Arg-α-CH–, 2‴, 4‴, 6‴a, 1″, 6‴b, 3″, 5″, Arg-CH_2– and 2×Eda-CH_2–), 2.57–2.63 (m, 1H, H_{eq}-2″), 1.70–1.93 (m, 3H, H_{ax}-2″ and Arg-CH_2–), 1.56–1.63 (m, 2H, Arg-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 177.74 (–C═O), 174.43 (–C═O), 162.04 (C-4), 159.41 (–C═NH), 150.94 (C-2), 148.88 (C-6), 97.74 (C-5), 96.75 (C-1‴ and 1′), 85.14 (C-4′), 75.28 (C-3′ and 2′), 75.02 (C-4″), 73.17 (C-4‴), 72.32 (C-6″ and 3‴), 70.94 (C-5″), 60.51 (C-2‴), 56.22 (Eda-CH_2–), 55.46 (Arg-α-CH– and C-1″), 50.71 (C-3″), 49.33 (C-5‴), 43.11 (C-6‴), 42.25 (Eda-CH_2–), 40.10 (Arg-CH_2–), 30.59 (C-2″ and Arg-CH_2–), 27.22 (Arg-CH_2–). HRMS calcd for $C_{29}H_{53}N_{13}O_{11}$ ([M+H]$^+$): 760.4060, found: 760.4067. $[\alpha]_D^{28.2}$ 1.265 (H_2O, c 0.076). λ_{max}=265 nm, ε=15,500.

*3.1.14.3. Compound **10q**.* Yield: 49% from **9q**, white foam. ^{1}H NMR (400 MHz, D_2O): δ 8.66 (s, 1H, H-8), 6.08 (d, 1H, J=3.0 Hz, H-1′), 5.56 (d, 1H, J=4.0 Hz, H-1‴), 4.78–4.87 (m, 2H, H-2′ and 3′), 4.58 (d, 1H, J=5.6 Hz, H-4′), 3.03–4.38 (m, 18H, H-5‴, H-3‴, 4″, 6″, Arg-α-CH–, 2‴, 4‴, 6‴a, 1″, 6‴b, 3″, 5″, Arg-CH_2– and 2×Eda-CH_2–), 2.58–2.63 (m, 1H, H_{eq}-2″), 1.88 (q, 1H, J=12.5 Hz, H_{ax}-2″), 1.57–1.79 (m, 2H, Arg-CH_2–), 1.38–1.50 (m, 2H, Arg-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 177.89 (–C═O), 175.00 (–C═O), 159.41 (–C═NH), 159.27 (C-6), 157.41 (C-2), 153.01 (C-4), 140.20 (C-5), 114.52 (C-8), 95.00 (C-1‴), 93.36 (C-1′), 85.60 (C-4′), 76.15 (C-3′), 75.36 (C-2′), 74.00 (C-4″), 73.37 (C-4‴), 72.37 (C-6″), 70.99 (C-3‴), 70.43 (C-5″), 60.71 (C-2‴), 56.52 (Eda-CH_2–), 55.52 (Arg-α-CH–), 53.50 (C-1″), 50.78 (C-3″), 49.42 (C-5‴), 43.19 (C-6‴), 42.33 (Eda-CH_2–), 40.04 (Arg-CH_2–), 30.54 (C-2″ and Arg-CH_2–), 27.35 (Arg-CH_2–). HRMS calcd for $C_{30}H_{53}N_{15}O_{11}$ ([M+H]$^+$): 800.4122, found: 800.4121. $[\alpha]_D^{28.9}$ 0.991 (H_2O, c 0.080). λ_{max}=252 nm, ε=10,050.

*3.1.14.4. Compound **10r**.* Yield: 54% from **9r**, white foam. ^{1}H NMR (400 MHz, D_2O): δ 8.35 (s, 1H, H-2), 8.19 (s, 1H, H-8), 6.18 (d, 1H, J=5.0 Hz, H-1′), 5.54 (d, 1H, J=3.6 Hz, H-1‴), 4.73–4.78 (m, 2H, H-2′ and 3′), 4.63 (d, 1H, J=4.0 Hz, H-4′), 3.04–4.34 (m, 18H, H-5‴, H-3‴, 4″, 6″, Arg-α-CH–, 2‴, 4‴, 6‴a, 1″, 6‴b, 3″, 5″, Arg-CH_2– and 2×Eda-CH_2–), 2.57–2.62 (m, 1H, H_{eq}-2″), 1.60–1.91 (m, 3H, H_{ax}-2″ and Arg-CH_2–), 1.41–1.50 (m, 2H, Arg-CH_2–). ^{13}C NMR (100 MHz, D_2O): δ 177.42 (–C═O), 174.81 (–C═O), 161.06 (–C═NH), 159.42 (C-6), 151.15 (C-4), 148.91 (C-2), 143.38 (C-8), 126.92 (C-5), 94.55 (C-1‴), 92.04 (C-1′), 85.94 (C-4′), 75.95 (C-3′), 75.61 (C-2′), 74.31 (C-4″), 73.20 (C-4‴), 72.46 (C-6″ and 3‴), 71.00 (C-5″), 60.47 (C-2‴), 56.29 (Eda-CH_2–), 55.57 (Arg-α-CH–), 53.06 (C-1″), 50.84 (C-3″), 49.57 (C-5‴), 43.07 (C-6‴), 42.35 (Eda-CH_2–), 40.37 (Arg-CH_2–), 30.71 (C-2″ and Arg-CH_2–), 27.35 (Arg-CH_2–). HRMS calcd for $C_{30}H_{52}N_{14}O_{11}$ ([M+H]$^+$): 785.4013, found: 785.4008. $[\alpha]_D^{29.0}$ 1.888 (H_2O, c 0.047). λ_{max}=250 nm, ε=12,000.

3.2. Determination of dissociation constants for the neamine–nucleoside conjugates binding to A site of 16S RNA and TAR RNA

The binding properties of neamine–nucleoside conjugates to A site of 16S RNA and TAR RNA were evaluated by SPR using Biacore 3000 instrument. Biotinylated A site of 16S and TAR RNA were purchased from Bioneer corporation of Korea. The biochip and the streptavidin were purchased from Biacore and Sigma, respectively. All the glass containers, pipette tips, eppendorf tubes and so on, which have been used in the experiment were pretreated to RNase free and keep not contaminated. All the solutions were prepared with RNase free water and filtered (pore size: 0.22 μm) before use. For preparing the streptavidin-functionalized (SA) biochip used in the assay, streptavidin in an acetate buffer solution (200 μg/mL, 60 μL) flowed through the surface of the carboxy-methyl dextran (CM-5) sensor chip and was covalently attached to the surface through the ethanolamine linkers. Biotinylated A site of 16S RNA and TAR RNA in HBS (HEPES-buffered saline, 10 mM HEPES, 100 mM NaCl, 0.1 mM EDTA, pH 6.8) buffer (0.1 OD/mL, 6 μL) was flowed through the surface and immobilized on the streptavidin-coated sensor chip and a solution with different concentrations of the neamine–nucleoside conjugates (160 μM, 80 μM, 40 μM, 20 μM, 10 μM, 5 μM, 2.5 μM, 1.25 μM, 0.625 μM, 0.3125 μM, …, 0 μM as blank control) in HBS buffer (10 mM HEPES, 150 mM NaCl, 3 mM EDTA, pH 7.4) was flowed through on the surface, the response units (RUs) for diverse concentrations were obtained and the dissociation constants (K_D) were determined by the curve fitting analysis according to the equation: $RU_{AG}=RU_{max}[AG]/K_D+[AG]$, among which $RU_{max}=RU_{RNA}(MW_{AG}/MW_{RNA})$. Where RU_{AG} is the response unit of the neamine–nucleoside conjugates, [AG] is the concentration of the neamine–nucleoside conjugates, RU_{max} is the expected maximum response unit value of the neamine–nucleoside conjugates. RU_{RNA} is the response unit of the immobilized A site of 16S RNA and TAR RNA on the biochip, MW_{AG} and MW_{RNA} are the molecular weights of the neamine–nucleoside conjugates and A site of 16S RNA and TAR RNA.

3.3. Procedures for the molecular docking study

AutoDock 3.0 program was used for the molecular docking procedure. The target structure of A site of 16S RNA was extracted from the protein databank (PDB code 1PBR). The ligands were minimized with AMBER force field using the steepest decent and conjugated gradient methods consecutively. The obtained optimized structures were used for the following docking.

The molecular docking calculations were carried out using an empirical free energy function and Lamarckian Genetic Algorithm. Each dihedral angle of ligands was chosen to be flexible. The number of generations, energy evaluation, and docking runs were set to 370,000, 1,500,000, and 50, respectively, and the kinds of atomic charges were taken as Kollman-all-atom for 16S RNA and Gasteiger–Hucel for the ligands.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.084.

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