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Synthesis of sugar–amino acid–nucleosides as potential glycosyltransferase inhibitors

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ABSTRACT

Sugar–amino acid–nucleosides (SAAN) were synthesized to mimic glycosyl nucleotide donors based on the hypothesis that a basic amino acid may interact with carboxylate groups of the enzyme in a manner similar to the diphosphate metal ion complex. C-Glycoside analogues of the D-galactopyranose or L-arabinofuranose ring systems, and four amino acids (lysine, glutamine, tryptophan, and histidine), were chosen for this study. The targets were synthesized and tested against GlfT2, a galactofuranosyltransferase essential for cell wall galactan biosynthesis in *Mycobacterium tuberculosis*. The inhibition assay showed that analogues containing histidine and tryptophan are moderate inhibitors of GlfT2.

1. Introduction

Glycosylation is an important biological process in all life forms ranging from bacteria to humans.[1] The majority of glycosyltransferases, the enzymes that make glycosidic bonds, involve sugar nucleotide donors, which all possess two negative charges presented either by diphosphates such as in UDP-Glc, UDP-Gal, UDP-GlcNAc, and GDP-Fuc or by one phosphate and one carboxylate in the case of CMP-NeuAc.[1,2] Structural analysis of enzyme–substrate complexes in glycosyltransferases has revealed that these negative charges often interact with enzyme motifs through a bivalent metal ion (e.g., Mn^{2+} and Mg^{2+}) bridge.[3] Inhibitors of glycosyltransferases are of therapeutic interest as potential anti-cancer agents, as well as for treatment of bacterial disease.[4] Consequently, numerous glycosyltransferase inhibitors have been designed and synthesized,[5] which has provided insights to the essential role played by the negative charges in sugar donors. In a systematic study using sialyl C-glycosides with different numbers of phosphate groups as sialyltransferase inhibitors, Schmidt and co-workers found that the monophosphate derivatives were weak inhibitors but derivatives with two phosphate groups were much better inhibitors, likely due to coordinated interaction.[6] However, one of the drawbacks of these charged inhibitors is their difficulty in being transported across the cell membrane. In order to improve the bioavailability, many studies focused on replacing the diphosphate group with non-charged entities including sulfone,[7] amide,[8] malonic and tartaric groups[9] as coordinators of metal ions have been reported. Unfortunately, most of these molecules display no significant activity against respective enzymes. We reasoned that replacement of the diphosphate moiety in sugar nucleotide donors by a basic amino acid may mimic the diphosphate–metal ion complex by direct interaction with the carboxylates in the catalytic site of the enzyme. In addition, these molecules may have better bioavailability than charged compounds.

In this report we describe the synthesis of C-α-D-galactopyranosyl–amino acid–uridine and C-α/β-L-arabinofuranosyl–amino acid–uridine derivatives as a new type of molecular architecture for glycosyltransferase inhibition. These compounds were then tested as potential inhibitors of a key galactosyltransferase (GlfT2), which is involved in cell wall galactan biosynthesis in *Mycobacterium tuberculosis*, the organism that causes the disease tuberculosis.[10,11] In addition, because *M. tuberculosis* infects alveolar macrophages in the lungs, the membrane transport properties of these compounds were investigated using macrophages.

2. Results and discussion

2.1. Synthesis of SAANs

Synthetic hybrids of sugar–amino acids (SAA)[12] and peptide nucleic acids (PNA)[13] are well known, hybrid molecules consisting of

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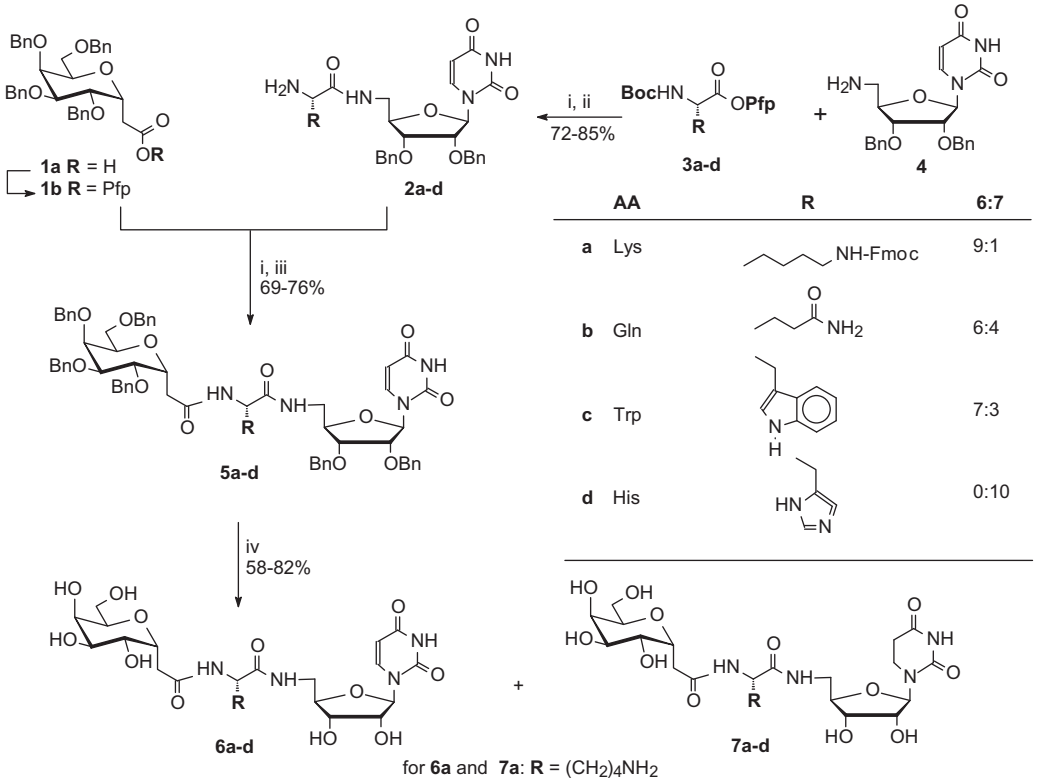
a sugar, an amino acid, and a nucleoside (SAAN) are another novel class of structures yet to be fully explored chemically and biologically although various amino acid–nucleoside substructures present in natural products.[14] Because the amino acid is placed between the sugar and the nucleoside, the synthesis of these hybrid molecules should be easily achieved by forming an amide bond between the moieties. Four basic amino acids (lysine, glutamine, tryptophan, and histidine), which are able to carry a positive charge, were chosen to mimic the diphosphate metal ion complex.

The starting C-galactoside acid (**1a**)[15] was prepared from the previously reported allyl C-galactoside[16] and 5′-amino-uridine derivative (**4**) was synthesized following known procedures.[17] The C-glycoside moiety provides the necessary stability to resist biodegradation. The SAAN can be assembled in two ways, by coupling the C-glycoside and amino acid followed by coupling with 5′-amino-uridine, or vice versa. We attempted both strategies using lysine as the amino acid and obtained poor coupling yield between the sugar amino acid and 5′-amino-uridine. In contrast, the reversed coupling sequence, using an activated C-glycoside ester for amide formation worked efficiently to give SAAN **5a–d** in good yield (Scheme 1). However, removal of *O*-benzyl groups by catalytic hydrogenation [H_2/Pd–C or $Pd(OH)_2$] under the atmospheric pressure was problematic with **5b** and **5d**. Incomplete de-O-benzylation, particularly on the uridine moiety, was observed. Although complete de-O-benzylation of **5a–c** was achieved under the conditions of H_2 and 10% Pd–C in 10% HOAc–MeOH for 3–4 days, the reduction of uridine C=C bond also occurred, resulting in an inseparable mixture of **6** and **7**. The ratio of **6**:**7** varies depending on the substrates (see Scheme 1). In the case of histidine derivative **5d**, complete removal of the *O*-benzyl groups required hydrogenation at 50 psi, which led to complete reduction of the uridine C=C double bond to afford **7d** as single product. Apparently, the structure of the amino acid side chain was able to affect significantly the catalytic hydrogenation process.

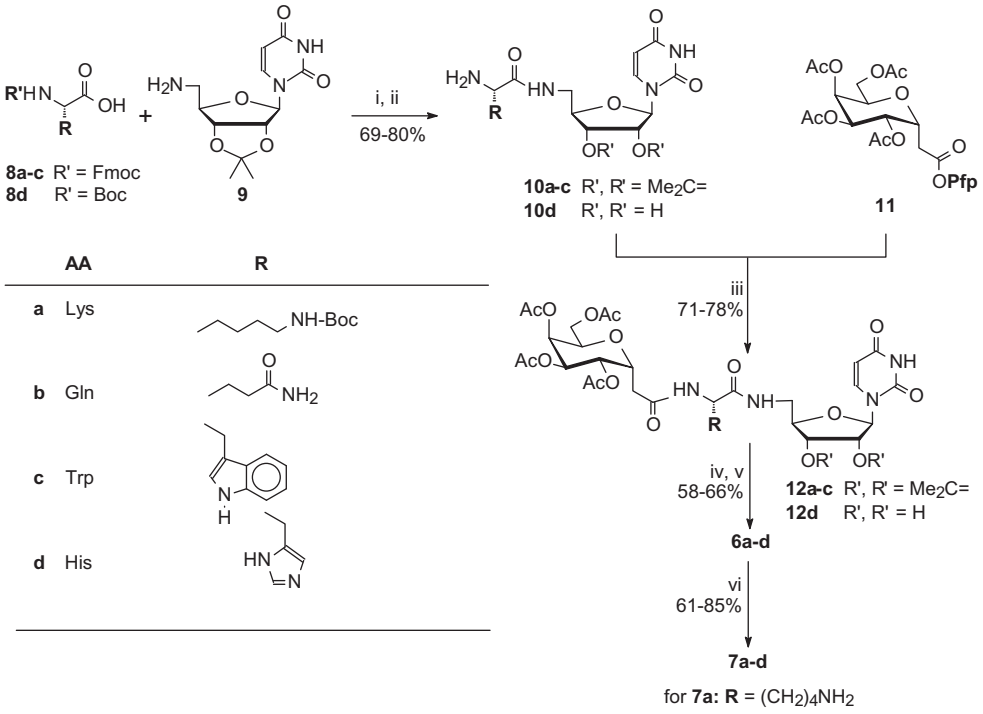
Because the uridine double bond was reduced by catalytic hydrogenation, we decided to avoid *O*-benzyl groups on both galactose and ribose to circumvent the problematic catalytic hydrogenation. Thus, the isopropylidenated uridine amine derivative **9**[18] and activated ester of per-O-acetylated *C*-galactosyl acid **11**[19] were prepared for coupling with the four amino acids (lysine, glutamine, tryptophan, and histidine). Amide bonds were formed first by condensation of the uridine amine with the amino acid, followed by removal of N^{α}-protecting groups (Fmoc or Boc) to afford **10a–d**, which were in turn coupled with **11** to give SAAN **12a–d** in 71–78% yield (see Scheme 2). Boc group deprotection of **8d** with TFA in CH_2Cl_2 also removed the isopropylidene acetal to give amide **10d**, which was coupled successfully with **11**. After global deprotection (TFA and then $NaHCO_3$–MeOH) and purification on a Bio-gel P-2 column, the desired *C*-galactosyl amino acid uridine derivatives (**6a–d**) were obtained in good yield (58–66%). In addition, to understand the importance of the uridine C=C bond for enzyme inhibition, **6a–d** were subjected to catalytic hydrogenation (H_2/Pd–C in water) to afford uridine-reduced analogues **7a–d**.

Although most galactosyltransferases use UDP-α-D-Gal*p*, the natural substrate of GlfT2 is UDP-α-D-Gal*f*. Therefore, SAANs with a D-*C*-galactofuranosyl moiety could be a better substrate mimic than the Gal*p* analogues. Because we had synthesized L-C-arabinofuranosides previously,[16] we explored this system as a surrogate of D-galactofuranose. D-Galactofuranose and L-arabinofuranose differ only in the side chain, appended to the ring at C4, with the latter being one carbon shorter.

In the preparation of the Ara*f* SAANs, we initially explored the use of *O*-acetyl protecting groups as was described above for the Gal*p* analogues. However, attempted 1-C-allylation using methyl 2,3,5-tri-*O*-acetyl-α-L-arabinofuranoside produced the undesired α-C-L-arabinofuranoside exclusively. To overcome this problem, benzyl ethers were used as the protecting groups. Subsequent 1-C-allylation of methyl 2,3,5-tri-*O*-benzyl-α-L-arabinofuranoside



Scheme 1. Reagents and conditions: (i) DMAP/DMF, rt, 12 h; (ii) TFA/CH_2Cl_2, 0 °C–rt, 2 h; (iii) piperidine/DMF, rt, 10 min (for Lys); (iv) H_2–Pd/C, 10% AcOH/MeOH, rt, 3–4 days.



Scheme 2. Reagents and conditions: (i) HOBt/EDC/DMF, rt, 6–12 h; (ii) piperidine, 10 min for **8a–c** or TFA/CH_2Cl_2, 0 °C–rt, 2 h for **8d**; (iii) DMAP/DMF, rt, 12 h; (iv) TFA:H_2O (9:1)/CH_2Cl_2, 0 °C–rt, 2 h; (v) $NaHCO_3$/MeOH, 5 min; (vi) Pd/C, H_2O, 6–12 h.

afforded a 1:1 isomeric mixture of C-arabinofuranosides, which were inseparable by silica gel column chromatography. Routine transformations were performed on known aldehyde[16] to obtain an activated ester **13** (see Supplementary data), which was also an inseparable isomeric mixture. Because the preliminary inhibition screening of Gal*p* analogues **6** and **7** showed that SAANs with tryptophan and histidine were active, those two amino acids were selected for coupling with uridine and the L-arabinofuranoside. The products resulting from the coupling of **13** with either **10c** or **10d** were separable by flash column chromatography and this provided pure isomers **14c,d** and **15c,d**, respectively. Their configurations were confirmed by 2D-NOESY experiments. Compounds **14c** and **15c** were treated with TFA to remove the isopropylidene acetal. The resultant intermediates, as well as **14d** and **15d**, were subjected to catalytic hydrogenation (H_2/Pd–C in 10% HOAc–MeOH) to produce products **16c,d** and **17c,d** (see Scheme 3). The final products were purified on a Bio-gel P-2 column. A portion of the above SAAN products was catalytically hydrogenated in water, to give the corresponding uridine-reduced products, **18c,d** and **19c,d**. This process generated an additional eight L-*C*-arabinofuranoside-based SAANs for screening against GlfT2.

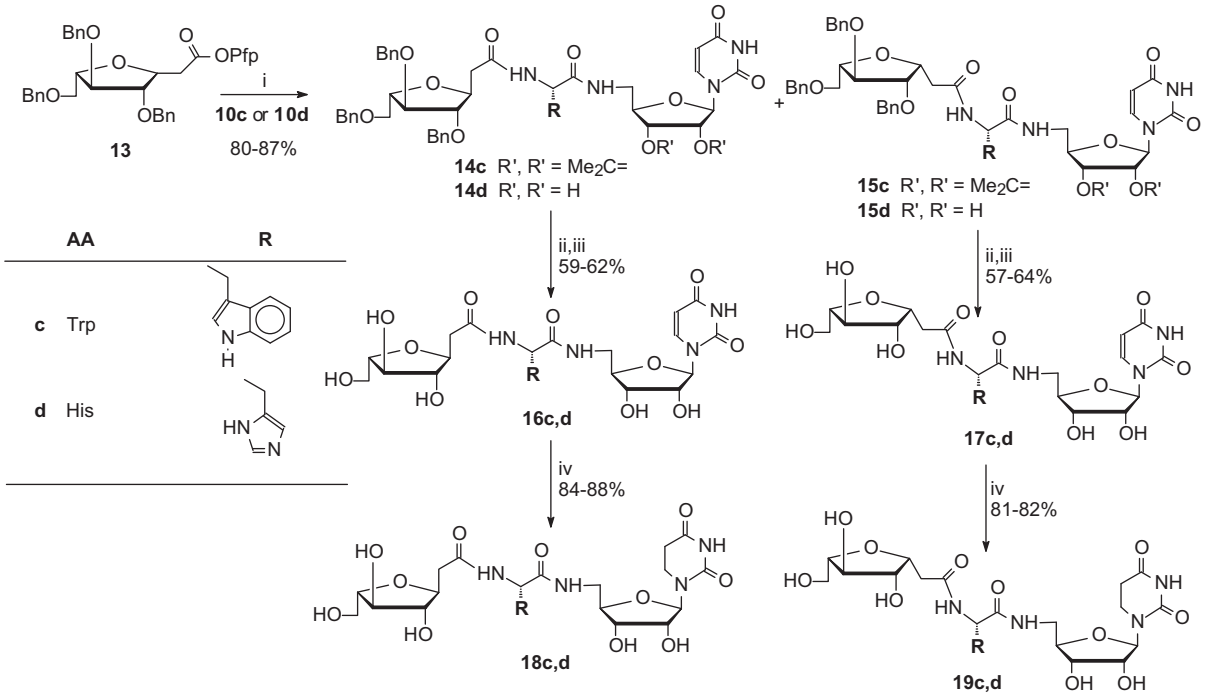
2.2. Inhibition evaluation

The ability of the compounds to inhibit GlfT2 was measured based on a coupled spectrophotometric assay method developed recently,[20] where a galactofuranosyl trisaccharide (β-D-Gal*f*-(1→5)-β-D-Gal*f*-(1→6)-β-D-Gal*f*-Octyl) was used as the acceptor. The *C*-galactosyl–amino acid–uridine analogues were initially screened at 4 mM against GlfT2 at pH 7.6. Under these conditions, tryptophan derivative **6c** showed 75% inhibition and histidine derivative **6d** showed 79% inhibition. To determine the approximate inhibition potency of these compounds, further titration experiments showed **6d** had an IC_{50} of 332 μM. However, the lysine **6a** and glutamine **6b** analogues showed only <12% inhibition at 4 mM. These results indicate that the SAANs containing tryptophan and histidine are moderate inhibitors of GlfT2 and the lysine and glutamine analogues are very weak inhibitors. Similarly, the *C*-arabinofuranosyl–amino acid–uridine derivatives were screened at 2 mM against GlfT2 at pH 7.6 and 6.0. The tryptophan derivative **17c** showed 30% inhibition at pH 7.6 whereas its isomer **16c** had only 8% inhibition. The histidine derivative **17d** was also a better inhibitor (37% inhibition) than its isomer **16d** (14% inhibition) at pH 7.6. All of the uridine-reduced analogues were not inhibitors (<10% inhibition at 2 mM). Table 1 summarizes the inhibition results. Unexpectedly, when the assay was carried out at pH 6.0, only **16d** was shown to be a weak inhibitor (24% inhibition) (data not shown). This could be a result of poor substrate mimic due to the charged amino acid, although a charged SAAN may be favored in transition state.

Efficient catalysis by enzymes requires the specific binding of substrates and the rapid release of the product(s). The substrate binding by glycosyltransferases is usually specific but not necessarily tight, with K_m values in the micromolar to low millimolar range. For example, kinetic characterization of GlfT2 using disaccharide and trisaccharide acceptors showed K_m values ranging from 204 μm to 1.7 mM, and tighter binding was observed for the trisaccharide receptors.[11] The IC_{50} obtained from inhibition by **6d** against GlfT2 in this study suggests a binding affinity comparable to K_m = 380 μM obtained from natural sugar donor (UDP-Gal*f*).[20] Inhibition of the enzyme appears to require proper interactions with the sugar, amino acid and uridine moieties because analogues having the similar molecular architecture, differing only in the side chain of the amino acid, did not effectively inhibit the enzyme.

The furanosyl analogues were only weak inhibitors of the enzyme, but the results were consistent with what we observed on pyranoside analogues that inhibition activity was associated with tryptophan and histidine in SAANs. In addition, the glycosyl configuration played a critical role. Only **17c** and **17d** appear to mimic the sugar donor and therefore acted as the moderate inhibitors.

The interaction of glycosyltransferases with the donor is a multiple binding process; the sugar moiety, the nucleoside, and the diphosphate all play critical roles. Sugar donor mimics resulting



Scheme 3. Reagents and conditions: (i) DMAP/DMF, 6 h; (ii) TFA:H_2O (9:1)/CH_2Cl_2, 0 °C–rt, 2 h for **10c**; (iii) H_2/Pd–C, AcOH/MeOH, rt, 24 h; (iv) H_2/Pd–C, H_2O, 6 h.

Table 1
Inhibition of GlfT2 activity by SAANs at pH 7.6

Compound	Inhibition% at 4 mM	Compound	Inhibition% at 2 mM
6a	11	**16c**	<10
6b	<10	**16d**	14
6c	75	**17c**	30
6d	79, IC_{50} = 332 μM	**17d**	37
7a	<10	**18c**	<10
7b	<10	**18d**	<10
7c	53	**19c**	<10
7d	18	**19d**	<10

from the replacement of the diphosphate with proper amino acids could not only provide similar interaction with enzyme carboxylate but also should not disrupt other interactions between enzyme and sugar moiety and nucleoside. The inhibition observed reflects the sum of these three interactions. Based on the results described here we propose that histidine and tryptophan are two amino acids that are likely able to mimic the carboxylate–diphosphate metal ion interaction. However, it should be noted that validation of this hypothesis requires further study.

2.3. Cross-cell membrane ability

The cross-cell membrane ability of molecules correlates to their bioavailability. Therefore, we examined the cross-membrane permeability of **6a–d** using the mouse macrophage cell line J774A.1 (ATCC TIB-67). A known TB drug, ethambutol, which inhibits arabinosyltransferases, was used as a positive control in the study. Macrophage cells were cultured with SAAN-containing medium (100 μM) for 2 min, 4.5 h, and 22 h. After removal of medium the cells were washed with PBS, sonicated and centrifuged through a 3 kDa filter to obtain sample solutions. The solutions were analyzed by multiple reaction monitoring (MRM) through MRM chromatograms and MS/MS analysis. Although stable in the medium as indicated by MRM and MS/MS, the permeability of these SAANs was, unfortunately, negligible under these conditions while ethambutol permeated reasonably well. The results suggest that even without charge, the hydrophilic sugar moiety is still a significant barrier for cell membrane crossing.

In conclusion, we report here a novel type of potential galactosyltransferase inhibitor by replacing the diphosphate moiety in sugar donor with a basic amino acid. Analogues containing tryptophan and histidine showed moderate inhibition against mycobacterial GlfT2, which we suggest may arise by mimicking the interaction between the diphosphate metal ion complex with the carboxylate residues present in the active site of the enzyme. However, the poor bioavailability of these compounds suggests that these molecules will likely only be useful as biological tools instead of therapeutics.

3. Experimental

3.1. General methods

^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a Varian instrument at 293 K. Chemical shifts are given in ppm downfield to the signal of internal TMS, and were assigned on the basis of 2D ^1H–^1H COSY and ^1H–^{13}C chemical-shift correlated experiments. In order to maintain consistency in NMR assignments carbon and proton numberings of the sugar were used despite the compounds being named otherwise. For high resolution mass spectroscopic analysis, samples were mixed with Agilent ES tuning mix for internal mass calibration and infused into an AB/MDS-Sciex (Concord, ON) QSTAR mass spectrometer at a flow-rate of 4 μL/min. All chemicals were purchased from Aldrich Co. and used without further purification.

3.2. Spectrophotometric inhibition assays

GlfT2 inhibition assays were performed in 384-array microtitre plate wells, which contained 100 mM MOPS, pH 7.6, 50 mM KCl, 20 mM $MgCl_2$, 1.1 mM NADH, 3.5 mM PEP, 3.75 U pyruvate kinase (PK, EC 2.7.1.40), and 16.8 U lactate dehydrogenase (LDH, EC 1.1.1.27). MOPS at pH 7.6, was added as a 20-fold stock solution. KCl, $MgCl_2$, and β-D-Gal*f*-(1→5)-β-D-Gal*f*-(1→6)-β-D-Gal*f*-Octyl

acceptor were dissolved in de-ionized distilled water (MQ). All other assay components were prepared in 100 mM MOPS, pH 7.6, with the exception of PEP, which, owing to its acidity, was buffered in 250 mM MOPS, pH 7.6. Stock solutions of NADH, PEP, PK, and LDH were made fresh on the day of use and all solutions were stored on ice. The final concentration of the compound was 2 mM. Test master mixes were prepared for 40 assays and stored on ice, then used for 10 test assays at a time. Likewise blanks were prepared for 12 reactions and 2 were used per run. Two compounds in triplicate and one set of controls in triplicate were included in each run. Reactions were initiated with the addition of 0.5 μg GlfT2 diluted in 100 mM MOPS. Closest duplicates of test and control reaction velocities were corrected by subtracting the mean blank velocity per run, and were expressed as a percentage of the mean control velocity.

Addition of 2.5 μL of diluted GlfT2 to the compound assay mixtures initiated each activity and inhibition test, bringing the final volume to 20 μL. Reactions were incubated at 37 °C and monitored at 340 nm at 10–15 s intervals using a Spectra Max 340PC microplate reader. Data were acquired using Softmax®PRO software operated in the Michaelis–Menten Protocol kinetic mode.

3.3. Permeability assay

J774 macrophage cells were grown in Dulbecco's modified medium (DMEM) which contained 10% FBS (fetal bovine serum), Hepes buffer and NEAA (non-essential amino acids). The cells were grown in 10 cm plates at 37 °C in a 5% CO_2/air incubator. Cells were passaged when 80–90% confluency was observed. The cells were washed with 10 mL of HBSS (Hank's balanced salt solution) to remove non-adherent cells. The cells were harvested using a rubber cell scrapper. These cells were split into three plates with approximately 2 million cells in each plate. The cell count was performed using hemocytometer.

J774 macrophage cells were seeded into Multiwell 24-well tissue culture plate. The cells were grown at 37 °C till confluency (4 days). The cell count was 1.7×10^5 for each well. Solutions (1 mM) of SAANs and ethambutol were filtered through a sterile 0.22 μM Millex-GV filter. Each compound was added to three wells to obtain a final concentration of 100 μM with 1 mL of total volume. The compounds and cells were incubated for 2 min, 4.5 h and 22 h before the medium was removed and the cells were washed with 2 mL PBS buffer three times. The cells become detached from the plate after washing with PBS. These cells were centrifuged for 10 min at 300g in a Centra CL3R Thermo IEC centrifuge and the cell pellet was washed again with PBS twice (2 mL) and centrifuged. The cells were then sonicated for 4 min with 40% power output. The cell lysate was then centrifuged through a 3 kDa MWCO Amicon centrifugal filter unit for 30 min at 3570g. The filtrate was collected and analyzed by mass spectrometer.

3.4. General procedure for the coupling of amino acids with uridine amine 9 followed by Fmoc deprotection

To a solution of the amino acid **8a–d** (1 mmol) in DMF were added HOBt (1 mmol), EDC (1 mmol) and uridine amine (1 mmol) and stirred for 6–12 h at room temperature. After completion of reaction, piperidine (5 mmol) was added and stirred for 10 min. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography to afford the corresponding amides **10a–d** in 69–80% yield.

3.5. General procedure for the coupling of amides 10a–d with 11

A solution of amide **10a–d** (1 mmol) in DMF was added to a solution of **11** (1 mmol) and catalytic amount of DMAP in DMF at room temperature, and the mixture was stirred overnight. After completion of reaction, the solvent was evaporated under reduced pressure. The residue was diluted with water and extracted with EtOAc (three times). The combined extracts were sequentially washed with saturated NH_4Cl solution, brine, dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by flash column chromatography to give pure compounds **12a–d** in 71–78% yield.

3.6. General procedure for deprotection of isopropylidene and acetate groups

A solution of 90% trifluoroacetic acid in water (1 mL) was added dropwise to a solution of the compound **12a–c** in CH_2Cl_2 at 0 °C, and the mixture was stirred for 2 h at room temperature. After completion of the reaction, the solvent and TFA were evaporated under vacuum. The residue was dissolved in methanol and passed through a pad of $NaHCO_3$ to deprotect the acetates. Similarly, the adduct **12d** was also deacetylated by passage through a pad of $NaHCO_3$. The filtrate was concentrated and the residue was loaded onto a column of Bio-gel P-2 (2×100 cm) and eluted with water. The fractions containing the product were pooled and lyophilized to afford **6a–d** in 58–66% yield.

3.7. General procedure for hydrogenation of the adducts 6a–d

To a solution of adducts **6a–d** (1 mmol) in water was added 10% Pd/C (0.1 mmol) and stirred under hydrogen atmosphere for 6–12 h. The reaction mixture was then filtered and washed with water and the aqueous solution was lyophilized to give the reduced analogues **7a–d** in 61–85% yield.

3.8. 5′-*N*-(N^{ε}-Boc-lysinamido)-5′-deoxy-2′,3′-*O*-isoporopylidene-uridine (10a)

Yield 79%; syrup; $[\alpha]_D$ −13 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 3H), 1.38–1.60 (m, 17H), 1.84 (br s, 1H), 3.09–3.18 (m, 2H), 3.32–3.40 (m, 1H), 3.50–3.58 (m, 1H), 3.65–3.76 (m, 1H), 4.15–4.21 (m, 1H), 4.70 (br s, 1H), 4.77 (dd, 1H, *J* = 5.6, 5.2 Hz), 5.09 (d, 1H, *J* = 5.2 Hz), 5.44 (s, 1H), 5.73 (d, 1H, *J* = 8.0 Hz), 7.24 (d, 1H, *J* = 8.0 Hz), 7.47 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9, 25.6, 27.4, 28.6 (2C), 29.8, 29.9, 34.5, 40.3, 40.6, 55.3, 79.5, 81.0, 83.9, 85.5, 96.2, 103.1, 115.0, 143.4, 150.5, 156.4, 163.3, 175.9; HRMS: calcd for $C_{23}H_{38}N_5O_8$ $[M+H]^+$ 512.2720, found 512.2722.

3.9. 5′-*N*-Glutaminamido-5′-deoxy-2′,3′-*O*-isopropylidene-uridine (10b)

Yield 80%; syrup; $[\alpha]_D$ +15 (*c* 0.5, H_2O); ^{1}H NMR (D_2O, 400 MHz) δ 1.41 (s, 3H), 1.61 (s, 3H), 1.86–1.98 (m, 2H), 2.33 (t, *J* = 7.6 Hz, 2H), 3.48 (t, 1H, *J* = 6.8 Hz), 3.52 (dd, 1H, *J* = 5.6, 14.4 Hz), 3.65 (dd, 1H, *J* = 7.2, 14.4 Hz), 4.30 (m, 1H), 4.88 (dd, 1H, *J* = 4.4, 6.4 Hz), 5.25 (dd, 1H, *J* = 2.4, 6.4 Hz), 5.81 (d, 1H, *J* = 2.4 Hz), 5.87 (d, 1H, *J* = 8.0 Hz), 7.66 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 24.5, 26.1, 30.0, 31.2, 40.8, 54.1, 81.4, 83.9, 84.6, 93.9, 102.2, 115.3, 144.3, 152.0, 167.5, 176.6, 178.4; HRMS: calcd for $C_{17}H_{26}N_5O_7$ $[M+H]^+$ 412.1832, found 412.1864.

3.10. 5′-*N*-Tryptophanamido-5′-deoxy-2′,3′-*O*-isopropylidene-uridine (10c)

Yield 69%; syrup; $[\alpha]_D$ −39 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 3H), 1.53 (s, 3H), 2.93 (dd, 1H, *J* = 8.4, 14.4 Hz), 3.31 (dd, 1H, *J* = 8.4, 14.4 Hz), 3.46–3.52 (m, 1H), 3.62–3.79 (m, 2H), 4.08–4.13 (m, 1H), 4.64 (dd, *J* = 4.8, 6.0 Hz, 1H),

4.91 (d, 1H, J = 6.4 Hz), 5.41 (s, 1H), 5.62 (d, 1H, J = 8.0 Hz), 7.01–7.18 (m, 4H), 7.32 (d, 1H, J = 8.0 Hz), 7.52 (br s, 1H), 7.61 (d, 1H, J = 8.0 Hz), 8.63 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.6, 27.4, 30.9, 40.7, 55.8, 81.2, 84.0, 85.6, 95.5, 102.8, 111.5, 114.9, 119.1, 119.6, 122.3, 123.6, 127.7, 136.4, 136.6, 143.2, 150.3, 163.7, 175.5; HRMS: calcd for $C_{23}H_{28}N_5O_6$ $[M+H]^+$ 470.2039, found 470.2054.

3.11. 5′-*N*-Hisditinamido-5′-deoxy-uridine (10d)

Yield 70%; syrup; $[\alpha]_D$ +2 (c 1, $CHCl_3$); ^{1}H NMR (CD_3OD, 400 MHz) δ 2.76 (dd, 1H, J = 7.2, 14.4 Hz), 2.96 (dd, 1H, J = 6.0, 14.8 Hz), 3.25–3.28 (m, 1H), 3.42–3.52 (m, 2H), 3.57 (dd, 1H, J = 6.4, 6.8 Hz), 3.90–3.96 (m, 2H), 4.15 (dd, 1H, J = 4.4 Hz), 5.67 (d, 1H, J = 4.4 Hz), 5.69 (s, 1H), 6.84 (s, 1H), 7.56 (s, 1H), 7.59 (d, 1H, J = 8.4 Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ 33.4, 41.7, 56.2, 72.0, 74.3, 83.5, 92.4, 102.8, 117.7, 134.8, 136.2, 143.2, 152.1, 165.9, 176.6; HRMS: calcd for $C_{15}H_{21}N_6O_6$ $[M+H]^+$ 381.1522, found 381.1512.

3.12. 5′-*N*-[N^{α}-(2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-D-*glycero*-L-*gluco*-heptit-1-yl-acetamido)-N^{ε}-Boc-lysinamido]-5′-deoxy-2′,3′-*O*-isopropylidene-uridine (12a)

Yield 71%; syrup; $[\alpha]_D$ −28 (c 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33–1.64 (m, 20H), 1.87–1.98 (m, 1H), 1.99–2.12 (m, 12H), 2.42 (dd, 1H, J = 4.0, 14.8 Hz), 2.54 (dd, 1H, J = 10.0, 14.8 Hz), 3.04–3.18 (m, 1H), 3.50–3.70 (m, 2H), 4.08–4.14 (m, 2H), 4.20–4.26 (m, 1H), 4.33–4.49 (m, 2H), 4.61–4.78 (m, 2H), 4.89 (dd, 1H, J = 2.0, 6.8 Hz), 5.16 (dd, 1H, J = 2.0, 6.8 Hz), 5.19 (s, 2H), 5.28 (s, 1H), 5.41 (s, 1H), 5.72 (d, 1H, J = 8.0 Hz), 6.87 (d, 1H, J = 8.4 Hz), 7.04 (s, 1H), 7.19 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 20.90, 20.91, 21.0, 22.4, 25.4, 27.4, 28.6, 29.7, 31.5, 35.9, 39.4, 40.2, 53.3, 60.6, 66.6, 67.8, 68.5, 68.6, 70.3, 79.7, 80.0, 83.9, 85.2, 97.1, 103.3, 115.1, 144.0, 151.1, 156.8, 163.3, 169.4, 169.7, 169.8, 170.0, 170.9, 172.4; HRMS: calcd for $C_{39}H_{58}N_5O_{18}$ $[M+H]^+$ 884.3776, found 884.3788.

3.13. 5-*N*-[N^{α}-(2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-D-*glycero*-L-*gluco*-heptit-1-yl-acetamido)-glutamido]-5-deoxy-2,3-*O*-isopropylidene-uridine (12b)

Yield 76%; syrup; $[\alpha]_D$ +26 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (s, 3H), 1.53 (s, 3H), 1.83–2.16 (m, 13H), 2.22–2.55 (m, 4H), 2.69 (dd, 1H, J = 10.0, 14.8 Hz), 3.44–3.50 (m, 1H), 3.69–3.76 (m, 1H), 4.07–4.29 (m, 4H), 4.53 (dd, 1H, J = 8.0, 8.4 Hz), 4.64–4.74 (m, 1H), 4.85 (dd, 1H, J = 6.0 Hz), 5.07–5.43 (m, 5H), 5.72 (d, 1H, J = 8.0 Hz), 6.62 (s, 1H), 7.05 (s, 1H), 7.21 (d, 1H, J = 8.0 Hz), 7.46 (d, 1H, J = 8.0 Hz), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 20.73, 20.77, 20.8, 25.3, 27.3, 29.2, 32.2, 34.6, 40.3, 52.7, 60.9, 67.0, 67.8, 67.9, 69.1, 69.4, 80.4, 84.1, 85.4, 96.3, 102.8, 114.7, 143.8, 150.7, 163.7, 169.8, 169.9, 170.0, 170.1, 170.7, 171.8; HRMS: calcd for $C_{33}H_{46}N_5O_{17}$ $[M+H]^+$ 784.2888, found 784.2876.

3.14. 5′-*N*-[N^{α}-(2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-D-*glycero*-L-*gluco*-heptit-1-yl-acetamido)-tryptophanamido]-5′-deoxy-2′,3′-*O*-isopropylidene-uridine (12c)

Yield 78%; syrup; $[\alpha]_D$ +23 (c 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 3H), 1.50 (s, 3H), 1.96 (s, 3H), 1.99 (s, 3H), 2.02 (s, 3H), 2.10 (s, 3H), 2.51 (dd, 1H, J = 4.8, 15.2 Hz), 2.61 (dd, 1H, J = 9.2, 15.6 Hz), 3.23 (d, 2H, J = 6.8 Hz), 3.38–3.56 (m, 2H), 4.03–4.18 (m, 3H), 4.36 (dd, 1H, J = 5.2 Hz), 4.69–4.74 (m, 1H), 4.76–4.88 (m, 1H), 5.14 (dd, 1H, J = 2.8, 8.8 Hz), 5.22–5.32 (m, 2H), 5.36 (s, 1H), 5.65 (d, 1H, J = 8.0 Hz), 6.90 (br s, 1H), 7.01 (d, 1H, J = 8.0 Hz), 7.04–7.17 (m, 4H), 7.29 (d, 1H, J = 8.0 Hz), 7.62 (d, 1H, J = 7.6 Hz), 8.77 (s, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 20.90, 20.92, 20.94, 25.6, 27.4, 28.7, 34.6, 41.2, 54.4, 61.2, 67.3, 68.1, 69.3, 69.5, 80.9, 83.7, 85.2, 96.6, 102.9, 110.5, 111.5, 114.9, 119.0, 119.7, 122.3, 123.7, 127.7, 136.4, 143.6, 150.5, 163.8, 169.6, 170.0, 170.2, 170.3, 170.9, 172.3; HRMS: calcd for $C_{39}H_{48}N_5O_{16}$ $[M+H]^+$ 842.3096, found 842.3129.

3.15. 5′-*N*-[N^{α}-(2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-D-*glycero*-L-*gluco*-heptit-1-yl-acetamido)-histidinamido]-5′-deoxy-uridine (12d)

Yield 77%; syrup; $[\alpha]_D$ +33 (c 1, CH_3OH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.06 (s, 3H), 2.08 (s, 3H), 2.09 (s, 3H), 2.19 (s, 3H), 2.69 (dd, 1H, J = 5.6, 15.6 Hz), 2.79 (dd, 1H, J = 9.2, 15.2 Hz), 3.06 (d, 1H, J = 8.4, 15.2 Hz), 3.18 (dd, 1H, J = 6.0, 14.8 Hz), 3.50–3.62 (m, 2H), 4.02–4.08 (m, 2H), 4.17 (dd, 1H, J = 4.8, 11.6 Hz), 4.22–4.38 (m, 3H), 4.59–4.68 (m, 2H), 5.24–5.34 (m, 2H), 5.44–5.48 (m, 1H), 5.77 (d, 1H, J = 4.4 Hz), 5.90 (d, 1H, J = 8.0 Hz), 7.11 (s, 1H), 7.62 (d, 1H, J = 8.0 Hz), 8.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.1, 20.17, 20.22, 20.3, 28.1, 33.7, 40.9, 53.8, 62.6, 68.0, 68.2, 69.9, 70.5, 71.9, 72.2, 73.2, 81.9, 90.8, 102.4, 117.0, 131.4, 135.2, 142.4, 151.6, 166.2, 172.1, 172.7, 172.9, 173.2, 173.4, 173.7; HRMS: calcd for $C_{31}H_{41}N_6O_{16}$ $[M+H]^+$ 753.2579, found 753.2566.

3.16. 5′-*N*-[N^{α}-(2,6-Anhydro-D-*glycero*-L-*gluco*-heptit-1-yl-acetamido)-lysinamido]-5′-deoxy-uridine (6a)

Yield 66%; solid; $[\alpha]_D$ +9 (c 1.6, H_2O); ^{1}H NMR (D_2O, 400 MHz) δ 1.33–1.50 (m, 2H), 1.53–1.83 (m, 4H), 2.66 (dd, 1H, J = 4.4, 15.2 Hz), 2.74 (dd, 1H, J = 10.4, 15.2 Hz) 2.94 (dd, 2H, J = 7.6, 15.2 Hz), 3.52–3.63 (m, 2H), 3.66–3.79 (m, 3H), 3.88 (dd, 1H, J = 5.6, 5.6 Hz), 3.98–4.14 (m, 4H), 4.28 (dd, 1H, J = 6.0, 6.0 Hz), 4.33–4.40 (m, 1H), 4.45–4.53 (m, 1H), 5.84 (d, 1H, J = 5.2 Hz), 5.87 (d, 1H, J = 8.0 Hz), 7.61 (d, 1H, J = 8.0 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 22.2, 26.6, 30.7, 32.5, 39.3, 41.0, 54.2, 61.2, 67.7, 69.0, 69.8, 70.9, 72.8, 73.1, 73.3, 81.8, 90.4, 102.7, 141.7, 155.7, 161.1, 174.0, 174.4; HRMS: calcd for $C_{23}H_{38}N_5O_{12}$ $[M+H]^+$ 576.2516, found 576.2509.

3.17. 5′-*N*-[N^{α}-(2,6-Anhydro-D-*glycero*-L-*gluco*-heptit-1-yl-acetamido)-glutamido]-5′-deoxy-uridine (6b)

Yield 65%; solid; $[\alpha]_D$ +6 (c 1, H_2O); ^{1}H NMR (D_2O, 400 MHz) δ 1.96–2.04 (m, 1H), 2.06–2.16 (m, 1H), 2.38 (t, 2H, J = 7.6 Hz), 2.67 (dd, 1H, J = 8.4, 15.2 Hz), 2.75 (dd, 1H, J = 10.4, 15.2 Hz), 3.53–3.91 (m, 7H), 3.99–4.16 (m, 3H), 4.30–4.39 (m, 2H), 4.44–4.54 (m, 1H), 5.83 (d, 1H, J = 5.6 Hz), 5.89 (d, 1H, J = 8.0 Hz), 7.64 (d, 1H, J = 8.0 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 27.1, 30.4, 31.2, 32.5, 41.0, 53.7, 61.4, 67.7, 69.0, 69.8, 70.8, 72.8, 73.1, 81.8, 90.5, 102.7, 141.8, 160.8, 163.3, 173.8, 174.0, 178.0; HRMS: calcd for $C_{22}H_{34}N_5O_{13}$ $[M+H]^+$ 576.2153, found 576.2136.

3.18. 5′-*N*-[N^{α}-(2,6-Anhydro-D-*glycero*-L-*gluco*-heptit-1-yl-acetamido)-tryptophanamido]-5′-deoxy-uridine (6c)

Yield 61%; solid; $[\alpha]_D$ +12 (c 0.5, H_2O); ^{1}H NMR (D_2O, 400 MHz) δ 2.61 (dd, 2H, J = 4.2, 14.0 Hz), 2.72 (dd, 1H, J = 10.4, 15.2 Hz), 3.15–3.33 (m, 3H), 3.45–3.56 (m, 2H), 3.68 (d, 2H, J = 6.0 Hz), 3.71–3.77 (m, 2H), 3.79–3.88 (m, 2H), 3.97–4.06 (m, 2H), 4.43–4.51 (m, 1H), 4.68 (dd, 1H, J = 6.0, 6.4 Hz), 5.51 (d, 1H, J = 4.0 Hz), 5.65 (d, 1H, J = 8.0 Hz), 7.07–7.26 (m, 4H), 7.42 (d, 1H, J = 8.0 Hz), 7.63 (d, 1H, J = 8.0 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 27.2, 32.3, 40.2, 55.2, 61.0, 67.7, 68.9, 69.7, 69.8, 72.6, 73.1, 73.2, 81.6, 90.1, 102.3, 108.9, 111.7, 118.5, 119.5, 122.2, 124.6, 126.9, 136.2,

141.4, 151.4, 166.2, 173.6, 173.8; HRMS: calcd for $C_{28}H_{36}N_5O_{12}$ $[M+H]^+$ 634.2360, found 634.2326.

3.19. 5′-*N*-[*N*$^{\alpha}$-(2,6-Anhydro-D-*glycero*-L-*gluco*-heptit-1-yl-acetamido)-histidinamido]-5′-deoxy-uridine (6d)

Yield 58%; solid; $[\alpha]_D$ +44 (*c* 1, H_2O); ^1H NMR (D_2O 400 MHz) δ 2.59 (dd, 1H, *J* = 4.0, 15.2 Hz), 2.70 (dd, 1H, *J* = 10.8, 15.2 Hz), 3.01 (dd, 1H, *J* = 7.6, 15.2 Hz), 3.08 (dd, 1H, *J* = 7.2, 15.2 Hz), 3.51 (dd, 2H, *J* = 4.0, 6.4 Hz), 3.63–3.70 (m, 2H), 3.73 (dd, 1H, *J* = 3.2 Hz), 3.83 (dd, *J* = 6.0, 6.8 Hz, 1H), 3.95–4.05 (m, 4H), 4.27 (dd, 1H, *J* = 4.8, 5.2 Hz), 4.39–4.47 (m, 1H), 4.59 (dd, 1H, *J* = 6.8, 7.6 Hz), 5.76 (d, 1H, *J* = 4.8 Hz), 5.88 (d, 1H, *J* = 8.0 Hz), 6.98 (s, 1H), 7.60 (d, 1H, *J* = 8.0 Hz), 7.76 (s, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 28.7, 32.3, 40.8, 54.3, 61.0, 67.7, 68.9, 69.8, 70.5, 72.7, 73.1, 73.2, 81.9, 90.5, 102.4, 117.4, 131.5, 135.8, 142.3, 151.7, 166.4, 173.3, 173.8; HRMS: calcd for $C_{23}H_{33}N_6O_{12}$ $[M+H]^+$ 585.2156, found 585.2147.

3.20. 5′-*N*-[*N*$^{\alpha}$-(2,6-Anhydro-D-*glycero*-L-*gluco*-heptit-1-yl-acetamido)-lysinamido]-5′-deoxy-6′,7′-dihydro-uridine (7a)

Yield 82%; solid; $[\alpha]_D$ +3 (*c* 0.5, H_2O); ^1H NMR (D_2O, 400 MHz) δ 1.35–1.53 (m, 2H), 1.62–1.88 (m, 4H), 2.62–2.81 (m, 4H), 2.92–3.03 (m, 2H), 3.42–3.59 (m, 5H), 3.66–3.80 (m, 4H), 3.87 (dd, 1H, *J* = 5.2, 5.6 Hz), 3.98–4.09 (m, 5H), 4.25–4.34 (m, 2H), 4.46–4.54 (m, 1H), 5.81 (d, 1H, *J* = 6.4 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 22.2, 26.7, 30.7, 32.5, 36.9, 37.7, 39.4, 41.2, 54.1, 61.2, 67.7, 68.9, 69.8, 70.2, 71.1, 72.8, 73.3, 81.2, 88.1, 155.8, 161.4, 174.1, 174.4; HRMS: calcd for $C_{23}H_{40}O_{12}$ $[M+H]^+$ 578.2673, found 578.2650.

3.21. 5′-*N*-[*N*$^{\alpha}$-(2,6-Anhydro-D-*glycero*-L-*gluco*-heptit-1-yl-acetamido)-glutamido]-5′-deoxy-6′,7′-dihydro-uridine (7b)

Yield 83%; solid; $[\alpha]_D$ +3 (*c* 2, H_2O); ^1H NMR (D_2O, 400 MHz) δ 1.93 (s, 3H), 1.98 (m, 1H), 2.06–2.18 (m, 1H), 2.39 (t, 2H, *J* = 7.6 Hz), 2.63–2.80 (m, 4H), 3.44–3.57 (m, 4H), 3.64–3.80 (m, 3H), 3.88 (dd, 1H, *J* = 5.2 Hz), 3.99–4.09 (m, 4H), 4.27–4.36 (m, 2H), 4.46–4.54 (m, 1H), 5.81 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 23.4, 27.2, 30.2, 31.2, 32.5, 36.9, 41.1, 53.6, 61.1, 67.7, 68.9, 69.8, 70.3, 70.9, 72.8, 81.2, 88.1, 160.9, 163.7, 173.8, 174.0, 178.0; HRMS: calcd for $C_{22}H_{36}N_5O_{13}$ $[M+H]^+$ 578.2309, found 578.2295.

3.22. 5′-*N*-[*N*$^{\alpha}$-(2,6-Anhydro-D-*glycero*-L-*gluco*-heptit-1-yl-acetamido)-tryptophanamido]-5′-deoxy-6′,7′-dihydro-uridine (7c)

Yield 61%; solid; $[\alpha]_D$ +5 (*c* 0.6, H_2O); ^1H NMR (D_2O, 400 MHz) δ 2.42–250 (m, 2H), 2.55–3.01 (m, 4H), 3.15–3.34 (m, 3H), 3.37–3.83 (m, 8H), 3.92–4.05 (m, 2H), 4.48 (m, 1H), 4.68 (m, 2H), 5.58 (d, 1H, *J* = 6.0 Hz), 7.15–7.30 (m, 3H), 7.50 (d, 1H, *J* = 7.6 Hz), 7.67 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 27.4, 30.1, 36.1, 40.1, 55.0, 61.0, 67.7, 68.9, 69.7, 69.8, 70.1, 72.6, 73.9, 78.4, 80.7, 87.9, 109.1, 112.0, 118.6, 119.5, 122.2, 124.6, 127.0, 136.3, 154.3, 173.5, 173.6, 173.8; HRMS: calcd for $C_{28}H_{38}N_5O_{12}$ $[M+H]^+$ 636.2517, found 636.2546.

3.23. 5′-*N*-[*N*$^{\alpha}$-(2,6-Anhydro-D-*glycero*-L-*gluco*-heptit-1-yl-acetamido)-histidinamido]-5′-deoxy-6′,7′-dihydro-uridine (7d)

Yield 85%; solid; $[\alpha]_D$ +8 (*c* 1, H_2O); ^1H NMR (D_2O, 400 MHz) δ 2.59 (dd, 1H, *J* = 4.0, 14.8 Hz), 2.68–2.77 (m, 3H), 3.00 (dd, 1H, *J* = 7.6, 15.2 Hz), 3.08 (dd, 1H, *J* = 6.8, 14.8 Hz), 3.39–3.51 (m, 5H), 3.64–3.78 (m, 3H), 3.86 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.90–4.05 (m, 4H), 4.19 (dd, 1H, *J* = 5.2, 6.0 Hz), 4.40–4.48 (m, 1H), 4.60 (dd, 1H, *J* = 7.2 Hz), 5.77 (d, 1H, *J* = 6.4 Hz), 6.98 (s, 1H), 7.70 (s, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 29.1, 30.2, 32.3, 36.9, 40.9, 54.4, 61.0, 67.7, 68.9, 69.8, 70.3, 70.7, 72.7, 73.1, 81.2, 88.1, 117.3, 131.4, 136.1, 151.6, 166.1, 173.4, 173.8; HRMS: calcd for $C_{23}H_{36}N_6O_{12}$ $[M+H]^+$ 587.2313, found 587.2304.

3.24. 5′-*N*-[*N*$^{\alpha}$-(2,5-Anhydro-3,4,5-tri-*O*-benzyl-L-glucit-1-yl-acetamido)-tryptophanamido]-5′-deoxy-uridine (14c)

Yield 87%; syrup; $[\alpha]_D$ −5 (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (s, 3H), 1.46 (s, 3H), 2.44 (dd, 1H, *J* = 3.6, *J* = 14.8 Hz), 2.65 (dd, 1H, *J* = 9.6, *J* = 15.2 Hz), 3.14 (dd, 1H, *J* = 6.8, *J* = 14.8 Hz), 3.20–3.33 (m, 2H), 3.44–3.60 (m, 3H), 3.80 (s, 1H), 3.94 (s, 1H), 3.98–4.02 (m, 1H), 4.30–4.55 (m, 9H), 4.68 (d, 1H, *J* = 6.8 Hz), 4.74 (m, 1H), 5.16 (s, 1H), 5.56 (d, 1H, *J* = Hz), 6.79 (br s, 1H), 6.85 (d, 1H, *J* = 8.0 Hz), 6.94–7.32 (m, 19H), 7.53 (d, 1H, *J* = 7.6 Hz), 8.34 (s, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 25.6, 27.4, 28.3, 40.5, 41.1, 54.3, 70.4, 71.9, 72.0, 73.6, 79.9, 80.5, 82.4, 83.7, 84.8, 84.9, 87.1, 95.9, 102.9, 110.2, 111.3, 114.9, 119.2, 119.5, 122.0, 124.2, 127.7, 127.9, 128.10, 128.12, 128.14, 128.2, 128.65, 128.66, 128.70, 136.2, 137.6, 137.7, 138.1, 143.2, 150.5, 163.5, 170.8, 172.6; HRMS: calcd for $C_{51}H_{56}N_5O_{11}$ $[M+H]^+$ 914.3976, found 914.3942.

3.25. 5′-*N*-[*N*$^{\alpha}$-(2,5-Anhydro-3,4,5-tri-*O*-benzyl-L-glucit-1-yl-acetamido)-histidinamido]-5′-deoxy-uridine (14d)

Yield 80%; syrup; $[\alpha]_D$ −16 (*c* 2, $CHCl_3$); ^1H NMR (CD_3OD, 400 MHz) δ 2.47 (dd, 1H, *J* = 4.0, 14.0 Hz), 2.60 (dd, 1H, *J* = 9.2, 14.0 Hz), 2.95 (dd, 1H, *J* = 8.8, 14.8 Hz), 3.13 (dd, 1H, *J* = 4.8, 14.8 Hz), 3.40–3.54 (m, 4H), 3.87–3.99 (m, 4H), 4.12–4.23 (m, 2H), 4.33–4.51 (m, 7H), 4.62 (dd, 1H, *J* = 6.4, 6.8 Hz), 5.66–5.74 (m, 2H), 6.99 (s, 1H), 7.16–7.30 (m, 15H), 7.56 (d, 1H, *J* = 8.0 Hz), 7.82 (s, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 29.7, 40.9, 42.1, 54.8, 71.3, 72.1, 72.8, 72.9, 74.3, 74.6, 81.6, 83.5, 83.8, 85.8, 88.1, 92.3, 103.2, 118.6, 128.83, 128.86, 128.9, 129.0, 129.1, 129.2, 129.4, 129.5, 133.5, 135.9, 139.1, 139.2, 139.4, 143.4, 152.4, 166.0, 173.0, 173.5; HRMS: calcd for $C_{43}H_{49}N_6O_{11}$ $[M+H]^+$ 825.3459, found 825.3449.

3.26. 5′-*N*-[*N*$^{\alpha}$-(2,5-Anhydro-3,4,5-tri-*O*-benzyl-L-mannit-1-yl-acetamido)-tryptophanamido]-5′-deoxy-uridine (15c)

Yield: 87%; syrup; $[\alpha]_D$ −11 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26 (s, 3H), 1.46 (s, 3H), 2.50 (dd, 1H, *J* = 4.4, 14.8 Hz), 2.62 (dd, 1H, *J* = 8.4, 14.8 Hz), 3.10–3.53 (m, 6H), 3.87 (s, 1H), 3.98–4.04 (m, 1H), 4.26–4.51 (m, 8H), 4.68 (d, 1H, *J* = 6.8 Hz), 4.76–4.82 (m, 1H), 5.31 (s, 1H), 5.56 (d, 1H, *J* = 8.0 Hz), 6.82 (d, 1H, *J* = 7.6 Hz), 6.91 (d, 1H, *J* = 8.0 Hz), 6.95–7.32 (m, 19H), 7.55 (d, 1H, *J* = 8.0 Hz), 8.52 (s, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 25.6, 27.4, 28.1, 36.8, 41.0, 54.2, 70.3, 71.7, 71.8, 73.4, 77.9, 80.7, 82.8, 83.1, 83.2, 83.8, 84.9, 95.0, 102.9, 110.4, 111.5, 115.0, 119.0, 119.6, 122.2, 123.7, 127.9, 127.8, 127.94, 127.97, 28.05, 128.08, 128.11, 128.2, 128.61, 128.67, 128.7, 136.3, 137.7, 137.8, 138.1, 143.0, 150.4, 163.7, 171.6, 172.5; HRMS: calcd for $C_{51}H_{56}N_5O_{11}$ $[M+H]^+$ 914.3976, found 914.3962.

3.27. 5′-*N*-[*N*$^{\alpha}$-(2,5-Anhydro-3,4,5-tri-*O*-benzyl-L-mannit-1-yl-acetamido)-histidinamido]-5′-deoxy-uridine (15d)

Yield 80%; syrup; $[\alpha]_D$ −2 (*c* 2.5, CH_3OH); ^1H NMR (CD_3OD, 400 MHz) δ 2.43 (dd, 1H, *J* = 4.0, 14.5 Hz), 2.68 (dd, 1H, *J* = 9.2, 14.0 Hz), 2.88 (dd, *J* = 8.8, 14.8 Hz), 2.96 (s, 1H), 3.11 (dd, 1H, *J* = 4.0, 14.8 Hz), 3.34–3.54 (m, 4H), 3.86–3.99 (m, 4H), 4.10–4.14 (m, 1H), 4.25–4.49 (m, 6H), 4.62 (dd, 1H, *J* = 4.8, 5.2 Hz), 5.72 (d, 1H, *J* = 8.0 Hz), 5.76 (d, 1H, *J* = 4.4 Hz), 6.83 (s, 1H), 7.13–7.30 (m, 15H), 7.35 (d, 1H, *J* = 8.0 Hz), 7.46–7.51 (m, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 30.1, 37.1, 41.8, 42.1, 50.0, 52.5, 55.2, 71.5, 71.8, 72.4,

72.7, 74.3, 74.7, 79.8, 83.7, 84.0, 84.1, 84.3, 92.0, 103.5, 118.6, 128.1, 128.82, 128.88, 128.9, 129.0, 129.2, 129.3, 129.50, 129.52, 133.6, 135.8, 129.9, 136.4, 139.2, 139.3, 139.4, 143.0, 145.4, 152.9, 166.7, 173.9, 174.0; HRMS: calcd for $C_{43}H_{49}N_6O_{11}$ $[M+H]^+$ 825.3459, found 825.3436.

3.28. 5′-*N*-[N^{α}-(2,5-Anhydro-L-glucit-1-yl-acetamido)-tryptophanamido]-5′-deoxy-uridine (16c)

Yield 59%; solid; $[\alpha]_D$ −29 (*c* 0.5, H_2O); ^1H NMR (D_2O, 400 MHz) δ 2.67 (dd, 2H, *J* = 5.6, 8.0 Hz), 3.26 (dd, 2H, *J* = 3.2, 6.8 Hz), 3.35 (dd, 1H, *J* = 3.2, 14.8 Hz), 3.50–3.57 (m, 2H), 3.70 (ddd, 2H, *J* = 3.6, 8.0, 12.0 Hz), 3.80 (dd, 1H, *J* = 4.4, 4.8 Hz), 3.86–3.95 (m, 2H), 3.96 (dd, 1H, *J* = 6.0, 6.4 Hz), 4.06 (dd, 1H, *J* = 6.0, 6.4 Hz), 4.12–4.18 (m, 1H), 4.67 (dd, 1H, *J* = 6.4, 7.2 Hz), 5.54 (d, 1H, *J* = 4.8 Hz), 5.70 (d, 1H, *J* = 8.0 Hz), 7.13–7.23 (m, 2H), 7.27 (s, 1H), 7.44 (d, 1H, *J* = 8.0 Hz), 7.66 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 27.1, 39.2, 40.2, 55.1, 61.2, 69.7, 73.2, 76.5, 79.1, 80.1, 81.6, 82.7, 90.2, 102.3, 108.9, 111.8, 118.5, 119.5, 122.2, 124.6, 126.9, 136.3, 141.5, 154.1, 172.9, 173.5, 174.0; HRMS: calcd for $C_{27}H_{33}N_5O_{11}Na$ $[M+Na]^+$ 626.2074, found 626.2086.

3.29. 5′-*N*-[N^{α}-(2,5-Anhydro-L-glucit-1-yl-acetamido)-histidinamido]-5′-deoxy-uridine (16d)

Yield 62%; solid; ^1H NMR (D_2O, 400 MHz) δ 2.59 (d, 2H, *J* = 6.4 Hz), 2.74 (dd, 1H, *J* = 6.8, 12.4 Hz), 3.06 (dd, 1H, *J* = 7.2, *J* = 14.8 Hz), 3.12 (dd, 1H, *J* = 6.0, 15.2 Hz), 3.46 (dd, 2H, *J* = 6.0, 6.8 Hz), 3.55 (d, 1H, *J* = 4.0 Hz), 3.64–3.81 (m, 3H), 3.91–4.07 (m, 4H), 4.21 (dd, 1H, *J* = 5.6 Hz), 4.30 (dd, 1H, *J* = 4.8, 4.8 Hz), 4.62 (dd, 1H, *J* = 6.4, 7.6 Hz), 5.77 (d, 1H, *J* = 4.4 Hz), 5.89 (d, 1H, *J* = 8.0 Hz), 6.99 (s, 1H), 7.60 (d, 1H, *J* = 8.0 Hz), 7.72 (d, 1H, *J* = 4.4 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 30.2, 35.7, 40.7, 54.2, 61.7, 70.3, 70.8, 73.2, 77.5, 78.1, 81.9, 85.0, 88.2, 90.5, 102.5, 117.9, 136.1, 142.4, 154.6, 166.5, 173.5, 173.6; HRMS: calcd for $C_{22}H_{31}N_6O_{11}$ $[M+H]^+$ 555.2051, found 555.2114.

3.30. 5′-*N*-[N^{α}-(2,5-Anhydro-L-mannit-1-yl-acetamido)-tryptophanamido]-5′-deoxy-uridine (17c)

Yield: 57%; solid; $[\alpha]_D$ −18 (*c* 1, H_2O); ^1H NMR (D_2O, 400 MHz) δ 2.60 (d, 2H, *J* = 6.8 Hz), 3.19–3.42 (m, 4H), 3.48–3.90 (m, 8H), 4.01–4.08 (m, 2H), 4.28–4.32 (m, 1H), 4.69 (dd, 1H, *J* = 6.8, 8.0 Hz), 5.57 (d, 1H, *J* = 4.0 Hz), 5.72 (d, 1H, *J* = 8.0 Hz), 7.13–7.29 (m, 4H), 7.45 (d, 1H, *J* = 8.0 Hz), 7.76 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 27.1, 35.7, 40.3, 55.0, 61.6, 69.8, 73.2, 77.5, 77.9, 78.1, 81.6, 85.0, 90.3, 102.4, 108.9, 111.8, 118.5, 119.5, 122.2, 124.6, 126.9, 136.2, 141.5, 152.4, 172.2, 173.4, 174.0; HRMS: calcd for $C_{27}H_{34}N_5O_{11}$ $[M+H]^+$ 604.2255, found 604.2280.

3.31. 5′-*N*-[N^{α}-(2,5-Anhydro-L-mannit-1-yl-acetamido)-histidinamido]-5′-deoxy-uridine (17d)

Yield 64%; solid; ^1H NMR (D_2O, 400 MHz) δ 2.58–2.78 (m, 2H), 3.05 (dd, 1H, *J* = 7.2, *J* = 12.4 Hz), 3.14 (dd, 1H, *J* = 6.4, 14.8 Hz), 3.44–3.50 (m, 2H), 3.55 (d, 1H, *J* = 4.8 Hz), 3.67 (dd, 1H, *J* = 6.8, 13.6 Hz), 3.74 (dd, 1H, *J* = 3.6, 12.4 Hz), 3.86–4.08 (m, 6H), 4.20 (dd, 1H, *J* = 5.2, 5.6 Hz), 4.28–4.32 (m, 1H, *J* = 4.8, 5.2 Hz), 4.61 (dd, 1H, *J* = 7.2 Hz), 5.77 (d, 1H, *J* = 4.4 Hz), 5.88 (d, 1H, *J* = 8.0 Hz), 7.01 (s, 1H), 7.62 (d, 1H, *J* = 8.0 Hz), 7.87 (s, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 30.2, 39.2, 40.8, 53.9, 61.3, 70.3, 70.5, 76.5, 79.0, 80.0, 82.0, 82.7, 90.6, 102.4, 117.7, 128.9, 136.2, 142.4, 151.7, 166.3, 173.0, 173.8; HRMS: calcd for $C_{22}H_{31}N_6O_{11}$ $[M+H]^+$ 555.2051, found 555.2068.

3.32. 5′-*N*-[N^{α}-(2,5-Anhydro-L-glucit-1-yl-acetamido)-tryptophanamido]-5′-deoxy-6′,7′-dihydro-uridine (18c)

Yield 88%; solid; $[\alpha]_D$ −51 (*c* 0.6, H_2O); ^1H NMR (D_2O, 400 MHz) δ 2.51 (dd, 2H, *J* = 6.4, 10.8 Hz), 2.66 (dd, 2H, *J* = 2.4, 5.2 Hz), 2.76–2.85 (m, 1H), 2.97 (m, 1H), 3.22–3.30 (m, 3H), 3.44–3.55 (m, 2H), 3.59 (dd, 1H, *J* = 6.4, 6.8 Hz), 3.64–3.82 (m, 4H), 3.88–3.92 (m, 1H), 3.97 (dd, 1H, *J* = 6.4, 6.0 Hz), 4.06 (dd, 1H, *J* = 6.0, 6.0 Hz), 4.12–4.18 (m, 1H), 4.68 (dd, 1H, *J* = 6.4, 6.0 Hz), 5.58 (d, 1H, *J* = 6.4 Hz), 7.17–7.22 (m, 1H), 7.21–7.29 (m, 2H), 7.52 (d, 1H, *J* = 8.0 Hz), 7.70 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 27.3, 30.1, 36.2, 39.2, 40.2, 55.0, 61.2, 69.7, 70.0, 76.5, 79.1, 80.1, 80.9, 82.7, 87.9, 109.0, 112.0, 118.6, 119.6, 122.2, 124.6, 126.9, 136.3, 154.4, 172.8, 173.7, 173.9; HRMS: calcd for $C_{27}H_{36}N_5O_{11}$ $[M+H]^+$ 606.2411, found 606.2377.

3.33. 5′-*N*-[N^{α}-(2,5-Anhydro-L-mannit-1-yl-acetamido)-histidinamido]-5′-deoxy-6′,7′-dihydro-uridine (18d)

Yield 84%; solid; $[\alpha]_D$ −12 (*c* 1.5, H_2O); ^1H NMR (D_2O, 400 MHz) δ 2.59 (d, 2H, *J* = 6.8 Hz), 2.70–2.78 (m, 2H), 3.02 (dd, 1H, *J* = 7.6, 14.8 Hz), 3.14 (dd, 1H, *J* = 6.0, 14.8 Hz), 3.42–3.52 (m, 4H), 3.68 (dd, 1H, *J* = 5.6, 12.8 Hz), 3.72–3.83 (m, 3H), 3.92–4.07 (m, 4H), 4.22 (dd, 1H, 1H, *J* = 6.0, 5.6 Hz), 4.28–4.32 (m, 1H), 4.63 (dd, 1H, *J* = 5.2, 6.0 Hz), 5.77 (d, 1H, *J* = 6.0 Hz), 7.02 (s, 1H), 7.80 (s, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 28.8, 30.2, 35.7, 36.9, 40.9, 54.0, 61.7, 70.3, 70.8, 77.5, 77.9, 78.1, 81.2, 85.0, 88.2, 117.1, 132.8, 136.0, 154.6, 173.4, 173.5, 173.8; HRMS: calcd for $C_{22}H_{33}N_6O_{11}$ $[M+H]^+$ 557.2207, found 585.2189.

3.34. 5′-*N*-[N^{α}-(2,5-Anhydro-L-mannit-1-yl-acetamido)-tryptophanamido]-5′-deoxy-6′,7′-dihydro-uridine (19c)

Yield 82%; solid; $[\alpha]_D$ −23 (*c* 0.7, H_2O); ^1H NMR (D_2O, 400 MHz) δ 2.54 (t, 2H, *J* = 6.4 Hz), 2.60 (d, 2H, *J* = 6.8 Hz), 2.84–2.92 (m, 1H), 3.03 (m, 1H), 3.18–3.37 (m, 3H), 3.47–3.56 (m, 2H), 3.63–3.84 (m, 6H), 4.01–4.07 (m, 3H), 4.28–4.32 (m, 1H), 4.72 (dd, 1H, *J* = 7.2, 7.6 Hz), 5.61 (d, 1H, *J* = 6.0 Hz), 7.19–7.29 (m, 3H), 7.52 (d, 1H, *J* = 7.6 Hz), 7.70 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 27.3, 30.2, 35.7, 36.3, 40.3, 54.9, 61.7, 69.9, 70.1, 77.5, 77.9, 78.1, 80.9, 85.0, 88.0, 109.0, 112.0, 118.6, 119.6, 122.2, 124.6, 126.9, 136.3, 154.4, 173.3, 173.7, 173.9; HRMS: calcd for $C_{27}H_{36}N_5O_{11}$ $[M+H]^+$ 606.2411, found 606.2468.

3.35. 5′-*N*-[N^{α}-(2,5-Anhydro-L-mannit-1-yl-acetamido)-histidinamido]-5′-deoxy-6′,7′-dihydro-uridine (19d)

Yield 81%; solid; $[\alpha]_D$ −38 (*c* 1.5, H_2O); ^1H NMR (D_2O, 400 MHz) δ 2.58–2.79 (m, 4H), 3.02 (dd, 1H, *J* = 7.6, 14.4 Hz), 3.11 (dd, 1H, *J* = 6.8, 14.8 Hz), 3.42–3.52 (m, 4H), 3.66 (dd, 1H, *J* = 5.6, 12.8 Hz), 3.73 (dd, 1H, *J* = 3.2, 12.4 Hz), 3.92–3.98 (m, 4H), 4.02–4.7 (m, 1H), 4.20 (dd, 1H, *J* = 5.2, 5.6 Hz), 4.30 (dd, 1H, *J* = 6.0, 5.6 Hz), 4.63 (dd, 1H, *J* = 6.8, 7.2 Hz), 5.77 (d, 1H, *J* = 6.4 Hz), 7.01 (s, 1H), 7.74 (s, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 28.9, 30.2, 36.9, 39.2, 40.9, 54.2, 61.3, 70.2, 70.7, 76.5, 79.0, 80.0, 81.2, 82.7, 88.1, 117.7, 133.7, 136.1, 154.6, 172.9, 173.5, 173.8; HRMS: calcd for $C_{22}H_{33}N_6O_{11}$ $[M+H]^+$ 557.2207, found 557.2190.

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Supplementary data

Supplementary data (experiment procedures for compounds **1b** and **13**; ^{1}H, ^{13}C NMR, and 2D spectra of compounds (**6**, **7**, **10**, **12**, **14**–**19**)) associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.11.044.

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