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Synthesis of C-4 and C-7 triazole analogs of zanamivir as multivalent sialic acid containing scaffolds

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Abstract—The relative reactivities of C-4 and C-7 azides derived from zanamivir were compared in cycloaddition reactions with a panel of alkynes. All of the reactions proceeded efficiently with no observable differences between primary and secondary azides. Significant rate differences were observed between several members of the alkyne panel. Most notably, a trialkyne derived from a 1,3,5-triazine core underwent complete reaction within 4 h, whereas an analogous trialkyne with an all carbon aromatic core required 18 h. These results suggest that the triazine core serves as an internal catalyst.

Keywords: Click; Zanamivir; C-7 Analog; C-4 Analog

1. Introduction

As part of our program directed toward the design and synthesis of sialic acid containing scaffolds,[1] we recently conducted experiments to probe the relative reactivities of C-4 and C-7 functionalized sialic acids. In particular, we were interested in capitalizing upon the demonstrated efficiency of copper catalyzed 1,3-dipolar cycloaddition. Recently, Li et al. reported the synthesis of C-4 triazole analogs of zanamivir (**1**).[2] These compounds were prepared from a C-4 azide derived from sialic acid and several alkyl and aryl alkynes. The reactions were catalyzed by copper sulfate and sodium ascorbate and proceeded at room temperature in an ethanol/water solution giving the desired products in yields ranging from 60% to 80%. The reaction times were not reported. Among the several compounds prepared, one derived from 3-hydroxy pentyne (**2**) was shown to be ~61% protective against infection by avian influenza virus, whereas zanamivir is ~86% protective in the same assay (Fig. 1). Modeling studies suggest that diminished activity results from fewer favorable interactions between the triazole ring and neuraminidase as compared to the guanidyl group of zanamivir.

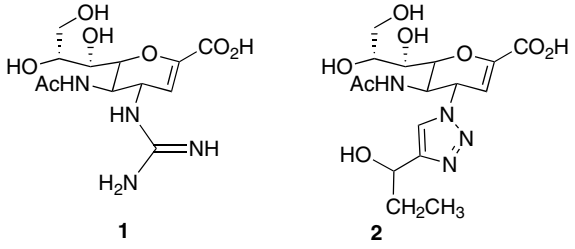

Figure 1. Zanamivir (**1**) and a C-4 analog (**2**).

Others have studied the antiviral effects of C-7 analogs of zanamivir.[3] According to X-ray studies of a neuraminidase/zanamivir complex reported by Varghese's group,[4] the 7-hydroxyl group of zanamivir forms no direct hydrogen bonds with neuraminidase. Additionally, it appears that groups attached to the C-7 hydroxyl would be oriented away from the enzyme active site, presenting a possible site for conjugation without affecting binding affinity. Among the many constructs that have been prepared, multivalent analogs are particularly promising. For example, dimeric zanamivir conjugates (**3**) have been reported to be potent, long-lasting inhibitors of several viral neuraminidase, including the recently identified H5N1 A/Chicken/Vietnam/8/2004 (Fig. 2).[3]

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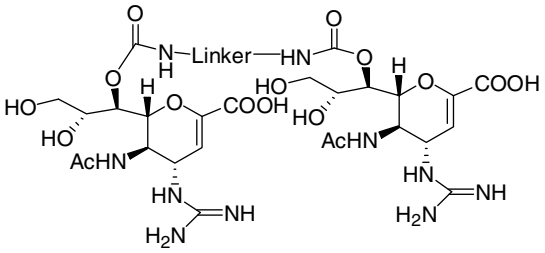


Figure 2. Dimeric zanamivir.

Highly potent and long-acting trimeric and tetrameric zanamivir analogs have also been synthesized and show long-lasting protective activity when tested in a mouse model (Fig. 3).[5] These compounds were prepared by amidation of polyvalent carboxylic acid cores with amines derived from a C-7 carbamate. Inspired by these studies and those of Li, vide infra, we have explored 1,3-dipolar cycloaddition as an alternative method of making polyvalent zanamivir constructs. At the same time, we were interested in understanding the relative reactivities of different alkyne systems, as this information is an important consideration in our long-term goals focused on functionalizing sialic acid containing oligomers for polyvalent ligand presentation. Presented herein are our synthetic studies of C-4 and C-7 cycloaddition reactions of zanamivir-derived azides and various mono- and trivalent alkynes.

2. Results and discussion

2.1. Synthesis of C-4 triazole analogs

The synthesis of the C-4 azide required for cycloaddition followed the published procedures of von Itzstein et al. (Scheme 1).[6] Commercially available sialic acid (**4**) was protected as a methyl ester and peracetylated by acetic anhydride, giving peracetylated *N*-acetylneuraminic acid methyl ester (**5**). Treatment of compound **5** with 3 equiv of TMSOTf gave oxazoline **6**, followed by reaction with azido trimethylsilane ($TMSN_3$) to afford peracetylated 4-azido-2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid methyl ester **7**. This key intermediate was subsequently reacted with the alkynes listed in Table 1. In a typical protocol, **7** was dissolved with the alkyne in a 1:1 mixture of H_2O and *tert*-butyl alcohol. Copper(II) sulfate pentahydrate was added, followed by sodium ascorbate. The mixture was stirred at room temperature for 1.5–18 h, as indicated to provide **8**–**16** after purification (Table 1). All of the reactions proceeded efficiently producing only the 1,4 substituted triazole, however, there were significant rate differences. In general, alkynes with oxygen containing appendages (entries 3–5) reacted faster than alkyl (entry 1) or halo (entry 2) alkynes even if the appendage is bulky (entries 3 and 4). As expected, the reaction with an alkyne conjugated to an amide (entry 7) proceeded relatively rapidly, as conjugation lowers the energy of the alkyne LUMO lowering the energy barrier.[7] In contrast, the reaction with an Fmoc-protected amine (entry 6) required 18 h. We were most surprised by the differences in the reaction rates for the trivalent alkynes, where all three alkynes of the cyanuric acid-derived core (entry 8) reacted in only 4 h and the analogous aryl core (entry 9) required 18 h. Sharpless and co-workers previously reported the use of these cores as dendrimer building blocks, but rate differences were not noted.[8] It is reasonable to expect copper chelation with the triazine core, which may accelerate the reaction by protecting copper I from oxidation.[8b] Chelation is also likely to lower the energy of the alkyne LUMO.

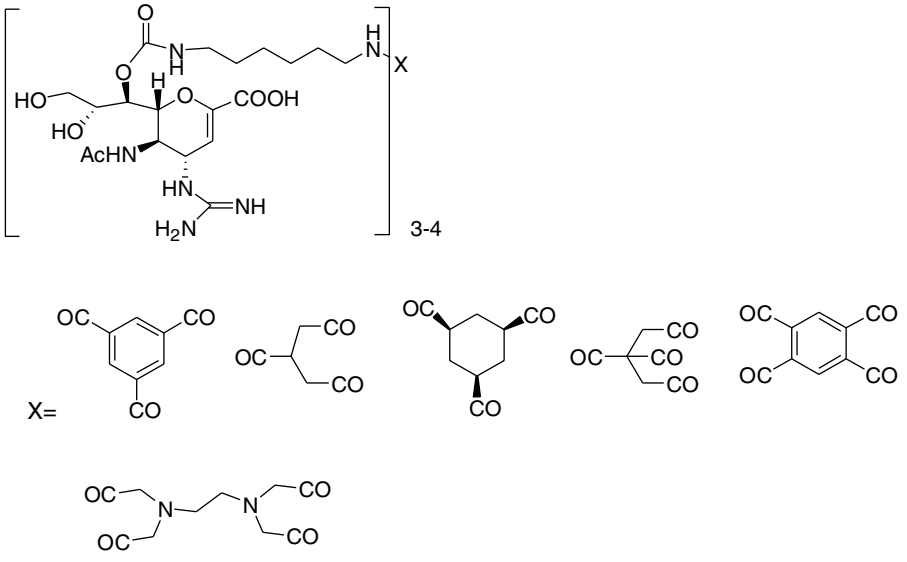
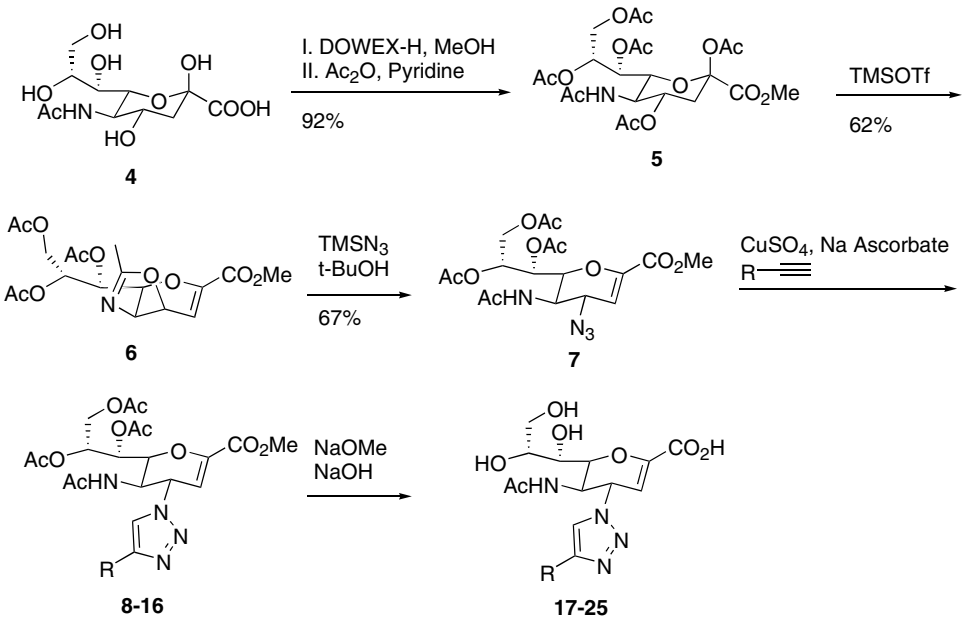


Figure 3. Trimeric and tetrameric zanamivir.



Scheme 1. Synthesis of C-4 analogs of zanamivir.

2.2. Synthesis of C-7 analogs of zanamivir

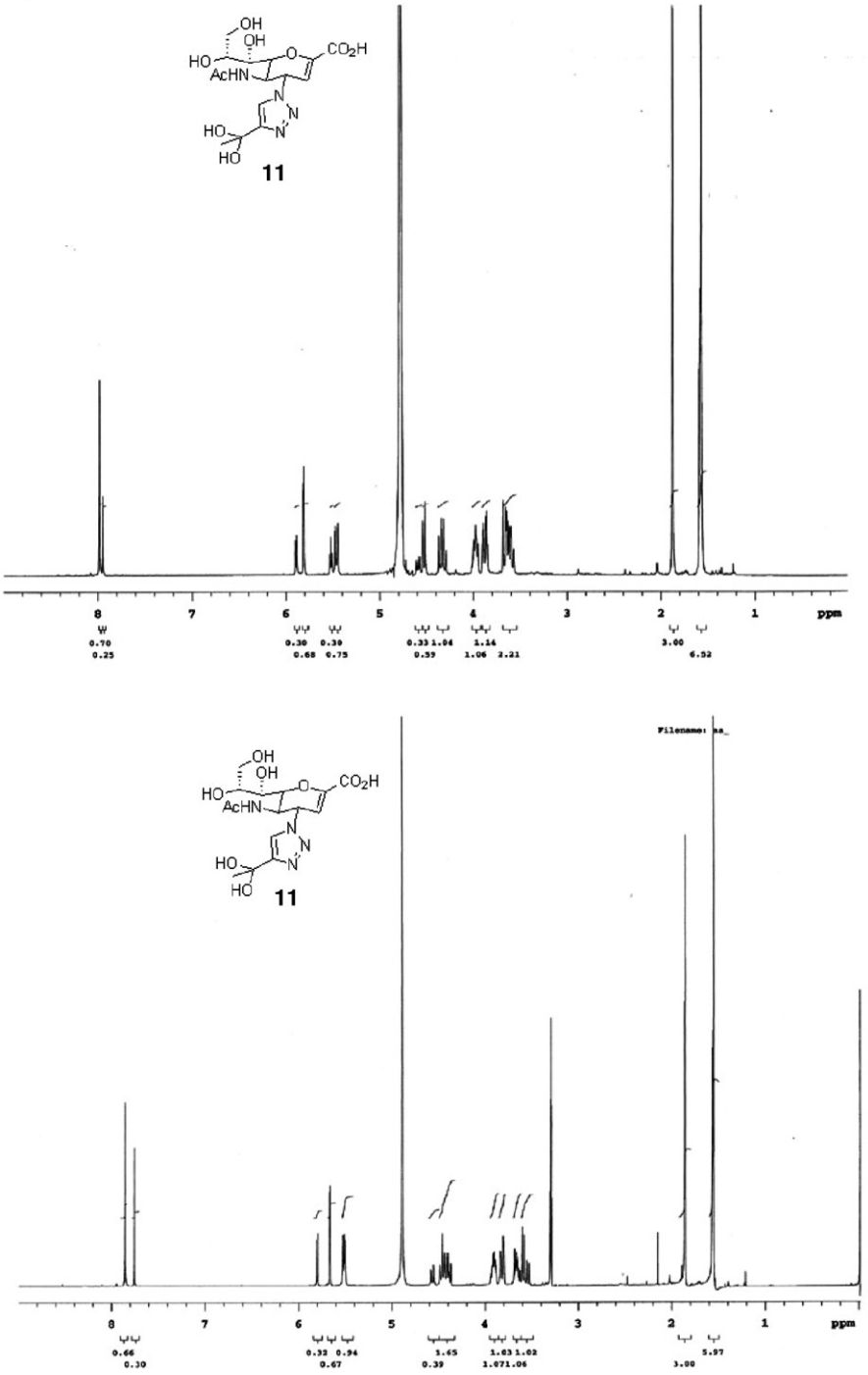
We next turned our attention to the synthesis of a C-7 azido analog following an analogous route to that reported by Honda and co-workers (Scheme 2).[3,9] Peracetylated 4-azido-2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid methyl ester (**7**) was hydrogenated with Lindlar catalyst to afford peracetylated 4-amino-2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid methyl ester **26**, subsequent treatment with *N*,*N*′-bis-(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine gave peracetylated 2-deoxy-2,3-dehydro-4-guanidino-*N*-acetylneuraminic acid methyl ester **27**. Deprotection of **27** with sodium methoxide followed by selective protection of the 8,9-dihydroxy groups with an isopropylidene gave compound **28**. The hydroxy group at the 7-position of compound **28** was activated using 4-nitrophenyl chloroformate and DMAP in dry pyridine to give **29**. Linker **31** was made from commercially available diaminotriethylene glycol **30** by selectively protecting one amino group as a *tert*-butoxycarbonyl (Boc), conversion of the free amino group to an azide and deprotection of the Boc with trifluoroacetic acid. Coupling between **29** and linker **31** gave intermediate **32** for further modification by cycloaddition.

The cycloaddition reactions were carried out under the same conditions reported for the C-4 analogs and the results of those reactions are shown in Table 2. Very similar results were obtained for the C-7 analogs. Consistent with the C-4 analog studies, the FMOC amine (entry 1) was sluggish whereas conjugation accelerated the rate (entry 2). Similarly, the 1,3,5-triazine core underwent cycloaddition in only 4 h (entry 3) whereas the aryl core required 18 h (entry 4). It is interesting to note that there was not any difference in rates between the C-4 and C-7 azides despite the apparent differences in steric hindrance.

The products of the cycloaddition reactions (**31**–**34**) were deprotected and purified by size exclusion chromatography to give **35**–**38**, respectively. In most cases, the compounds existed as rotameric mixtures in solution as evidenced by H NMR data. For example, switching solvent from D_2O to CD_3OD for compound **11** changed the ratio between two rotamers from 1:3 to 1:2 (according to integration of proton in the triazole ring at around 8.0 ppm in D_2O and 7.8 ppm in CD_3OD).

3. Summary

C-4 and C-7 azido analogs of zanamivir were prepared and subjected to 1,3-dipolar cycloaddition with various alkynes. The reactions were conducted at room temperature in a 1:1 mixture of H_2O and *tert*-butyl alcohol in the presence of copper(II) sulfate pentahydrate and sodium ascorbate. Alkyl, halo, amino, amido, ester, and alcohol containing mono-alkynes were surveyed in addition to ether containing trialkynes. All of the reactions proceeded efficiently and the results did not vary as a function of the azide, that is, there was no noticeable rate difference between the secondary C-4 azide as compared to the primary C-7 azide. Moreover, the reaction was compatible with the protected guanidyl functionality present in the C-7 azide. However, significant rate differences were observed between the alkynes. Most notably, a trivalent alkyne derived from 1,3,5-tri-



azine required only 4 h for all three alkynes to undergo cycloaddition, whereas the analogous trialkyne attached to an aryl core required 18 h suggesting that the heteroatomic triazine core may serve as an internal catalyst.

While the products of these cycloaddition reactions may be of general interest to the scientific community for further biological evaluation, our motivation for conducting these studies was to determine which alkynes would be most suitable for cycloaddition with C-4 and C-7 azido analogs of sialic acid. As noted above, we have a program dedicated to the design and synthesis of sialic acid containing oligomers, which have been shown to have stable structures in solution. In developing these conjugates further, we are interested in making stable scaffolds that can be functionalized with biologically relevant ligands. It occurred to us that 1,3-dipolar cycloaddition may be particularly well suited for such endeavors owing to the compatibility of the reaction in

Table 1. Cycloaddition reactions of C-4 analogs

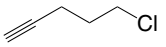
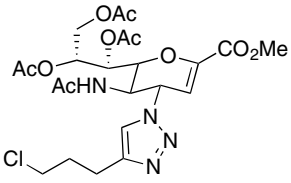
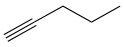
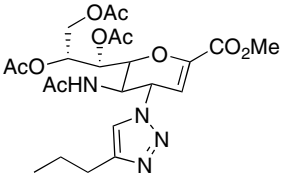
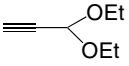
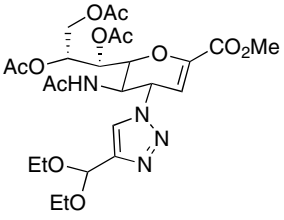
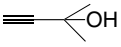
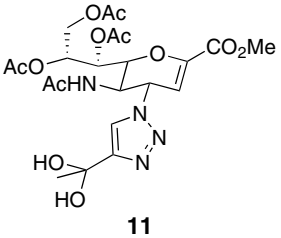
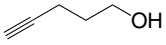
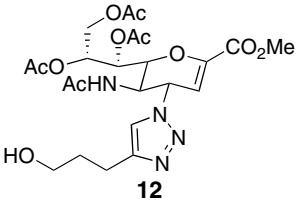
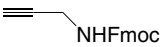
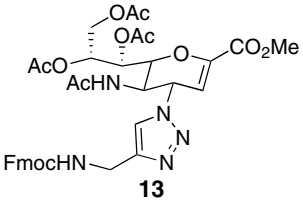
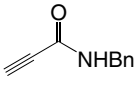
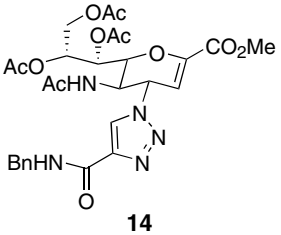
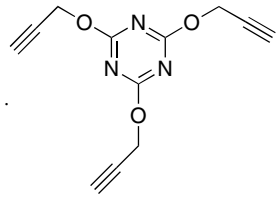
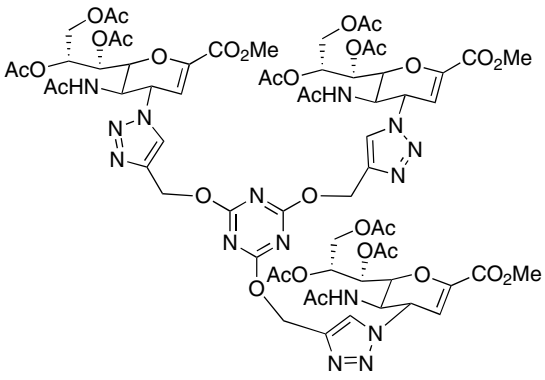
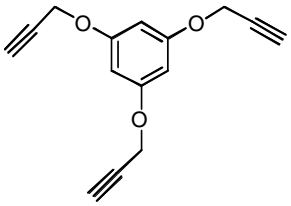
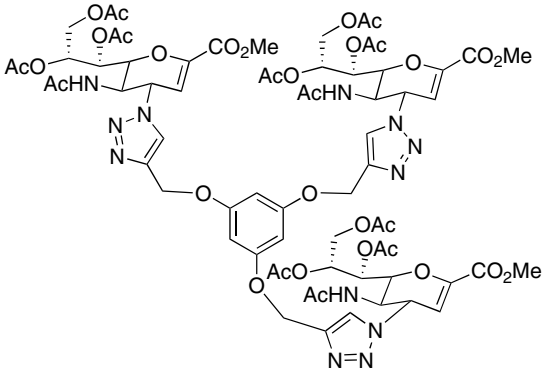
Entry	Alkyne	Product	Time (h)	Yield (%)
1		 **8**	4	83
2		 **9**	4	84
3		 **10**	1.5	63
4		 **11**	1.5	80
5		 **12**	1.5	82
6		 **13**	18	69
7		 **14**	2	81

Table 1 (*continued*)

Entry	Alkyne	Product	Time (h)	Yield (%)
8		 **15**	4	87
9		 **16**	18	85

biological settings.[10] The studies reported herein support the hypothesis that Click chemistry may be a viable approach toward scaffold functionalization, particularly for heteroatom containing alkynes.

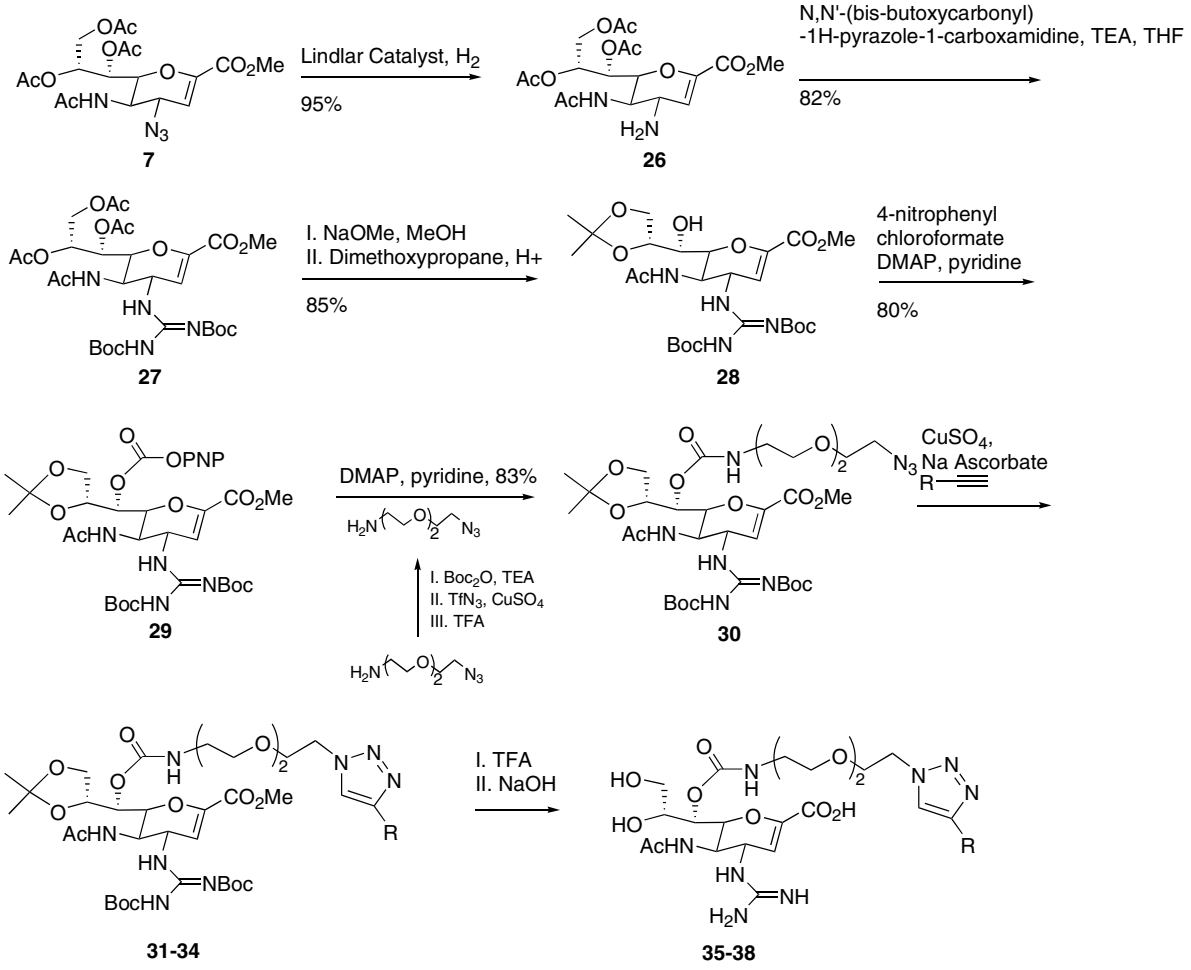
4. Experimental

4.1. Reagents and general methods

All chemicals were used as supplied without further purification. Dowex 50WX8 (200 mesh) acidic resin was purchased from Aldrich, washed with MeOH, and used without further purification. NaOMe–MeOH (0.5 M) was purchased from Aldrich. Glass-backed EM Science TLC plates (silica gel 60 with a 254 nm fluorescent indicator) were purchased from VWR International, cut into 2 cm × 5 cm portions, used without further manipulation, and stored over desiccant. Developed TLC plates were visualized under a short wave UV lamp, stained with a cerium–molybdate solution and charred. Column chromatography was conducted using flash silica gel (32–63 μm) available from Scientific Adsorbents and solvents were purchased from EM Science. ^{1}H NMR experiments were conducted on Inova 400 MHz spectrometers at 298 K. MS experiments were carried out on Finnigan LCQ DECA ESI-MS. IR were measured on Mattson Galaxy Series FTIR 3000.

4.2. 5-Acetylamino-4-[4-(3-chloro-propyl)-[1,2,3]triazol-1-yl]-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (8)

5-Acetylamino-4-azido-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester **7** was made by reported methods.[6] 5-Acetylamino-4-azido-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester **7** (50 mg, 0.11 mmol) and 5-chloro-pent-1-yne (15 μL, 0.14 mmol) were dissolved in 2 mL 1:1 mixture of H_2O and *tert*-butyl alcohol. Copper(II) sulfate pentahydrate (1.5 mg, 7.57 μmol) was added, followed by sodium ascorbate (0.04 mL of



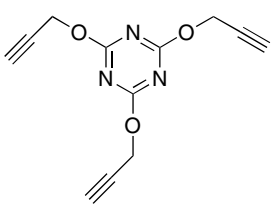
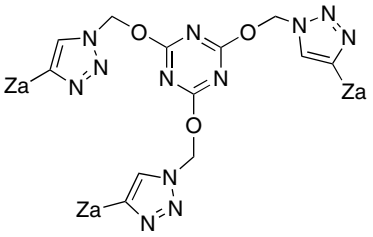
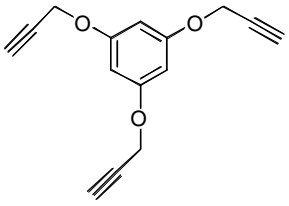
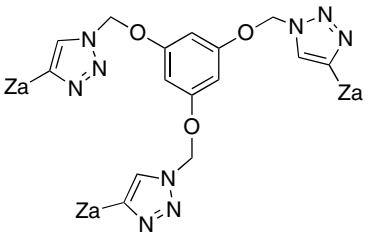
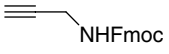
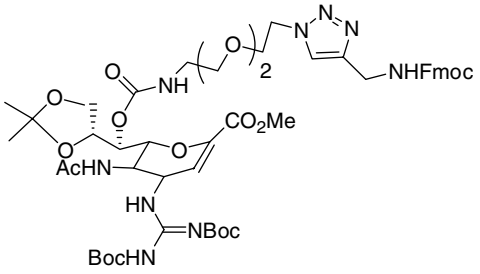
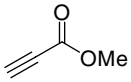
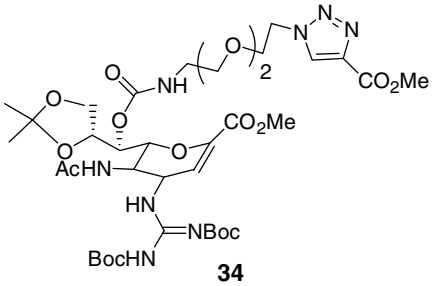
Scheme 2. Synthesis of C-7 analogues of zanamivir.

freshly prepared 1 M solution in water). The mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% NH_4OH followed by brine. Concentration afforded crude product. Further purification was performed by silica gel chromatography (EtOAc), giving compound **8** (83%). TLC (EtOAc): $R_f = 0.26$. ^1H NMR (400 MHz, $CDCl_3$, major rotamer) δ 7.45 (1H, s, triazole), 6.71 (1H, d, $J = 9.2$ Hz, NH), 6.02 (1H, d, $J = 2.4$ Hz, H-3), 5.74 (1H, dd, $J = 2.4$, 10.0 Hz, H-4), 5.54 (1H, dd, $J = 2.0$, 5.2 Hz, H-6), 5.40 (1H, m, H-5), 4.74 (1H, dd, $J = 2.0$, 5.2 Hz, H-7), 4.71 (1H, dd, $J = 2.0$, 12.8 Hz, H-9), 4.32 (1H, $J = 7.2$, 12.8 Hz, H-9′), 4.18 (1H, m, H-8), 3.82 (3H, s, OCH_3), 3.55 (2H, t, $J = 6.4$ Hz, CH_2Cl), 2.86 (2H, t, $J = 7.6$ Hz, CH_2), 2.12 (2H, m, CH_2), 2.08 (3H, s, OAc), 2.07 (3H, s, OAc), 2.06 (3H, s, OAc), 1.80 (3H, s, NAc). ^{13}C NMR (100 MHz, benzene-d_6, all rotamers) δ 170.6, 170.5, 170.4, 170.1, 161.6, 147.2, 146.3, 120.2, 107.9, 78.1, 72.3, 68.4, 62.9, 59.3, 52.3, 47.7, 44.0, 32.2, 22.9, 22.84, 22.75, 20.7, 20.6, 20.53, 20.48. IR: (cm^{-1}) 1744, 1665, 1534, 1438, 1371, 1220. ESIMS *m/z* calcd for $C_{23}H_{32}ClN_4O_{10}$ $[M+H]^+$: 559.17, found: 559.22.

4.3. 5-Acetylamino-4-(4-propyl-[1,2,3]triazol-1-yl)-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (9)

5-Acetylamino-4-azido-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester **7** (50 mg, 0.11 mmol) and pentyne (14 μL, 0.14 mmol) were dissolved in 2 mL 1:1 mixture of H_2O and *tert*-butyl alcohol. Copper(II) sulfate pentahydrate (1.5 mg, 7.57 μmol) was added, followed by sodium ascorbate (0.04 mL of freshly prepared 1 M solution in water). The mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% NH_4OH followed by brine. Concentration afforded crude product. Further purification was performed by silica gel chromatography (EtOAc), giving compound **9** (84%). TLC (EtOAc): $R_f = 0.24$. ^1H NMR (400 MHz, $CDCl_3$, major rotamer) δ 7.34

Table 2. Cycloaddition of C-7 azides

Entry	Alkynes	Products	Time (h)	Yield (%)
1		 **31**	4	69
2		 **32**	18	85
3		 **33**	18	87
4		 **34**	2	83

(1H, s, triazole), 7.24 (1H, d, $J = 9.2$ Hz, NH), 5.99 (1H, $J = 2.4$ Hz, H-3), 5.74 (1H, dd, $J = 2.4$, 10.0 Hz, H-4), 5.54 (1H, dd, $J = 1.6$, 5.2 Hz, H-6), 5.38 (1H, m, H-5), 4.75 (1H, dd, $J = 2.4$, 5.2 Hz, H-7), 4.71 (1H, dd, $J = 2.4$, 12.4 Hz, H-9), 4.32 (1H, dd, $J = 9.6$, 12.4 Hz, H-9′), 4.16 (1H, m, H-8), 3.80 (3H, s, OCH_3), 2.60 (2H, t, $J = 7.6$ Hz, CH_2), 2.06 (3H, s, OAc), 2.04 (3H, s, OAc), 2.03 (3H, sOAc), 1.78 (3H, s, NAc), 1.62 (2H, dd, $J = 7.2$, 14.8 Hz, CH_2), 0.91 (3H, q, $J = 7.6$ Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, all rotamers) δ 170.94, 170.92, 170.5, 170.1, 161.5, 148.6, 145.8, 119.9, 107.7, 77.0, 71.1, 67.8, 62.3, 58.2, 52.8, 48.2, 27.6, 22.9, 22.7, 21.0, 20.9, 20.8, 13.8. IR: (cm^{-1}) 1744, 1684, 1668, 1549, 1436, 1371, 1218. ESIMS *m/z* calcd for $C_{23}H_{32}N_4NaO_{10}$ $[M+Na]^+$: 547.20, found: 547.35.

4.4. 5-Acetylamino-4-(4-diethoxymethyl-[1,2,3]triazol-1-yl)-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (10)

5-Acetylamino-4-azido-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester **7**

(50 mg, 0.11 mmol) and 3,3-diethoxypropyne (21 μL, 0.14 mmol) were dissolved in 2 mL 1:1 mixture of H_2O and *tert*-butyl alcohol. Copper(II) sulfate pentahydrate (1.5 mg, 7.57 μmol) was added, followed by sodium ascorbate (0.04 mL of freshly prepared 1 M solution in water). The mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% NH_4OH followed by brine. Concentration afforded crude product. Further purification was performed by silica gel chromatography (1:20 MeOH–CH_2Cl_2), giving compound **10** (63%). TLC (1:20 MeOH–CH_2Cl_2): $R_f = 0.38$. ^1H NMR (400 MHz, $CDCl_3$, major rotamer) δ 7.67 (1H, s, triazole), 6.01 (1H, d, $J = 2.4$ Hz, H-3), 5.82 (1H, dd, $J = 2.4$, 10.0 Hz, H-4), 5.64 (1H, s, NH), 5.55 (1H, dd, $J = 2.0$, 5.3 Hz, H-6), 5.42 (1H, m, H-5), 4.86 (1H, m, H-7), 4.72 (1H, dd, $J = 2.4$, 12.4 Hz, H-9), 4.32 (1H, dd, $J = 9.6$, 12.4 Hz, H-9′), 4.18 (1H, m, H-8), 3.82 (3H, s, OCH_3), 3.53–3.58 (4H, m, OCH_2), 2.07 (3H, s, OAc), 2.05 (3H, s, OAc), 2.04 (3H, s, OAc), 1.84 (3H, s, NAc), 1.19 (6H, t, $J = 6.8$ Hz, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$, all rotamers) δ 171.0, 170.9, 170.3, 170.0, 161.4, 147.1, 146.0, 129.1, 128.3, 121.7, 107.3, 96.2, 76.7, 70.9, 67.8, 62.3, 61.5, 61.3, 58.1, 52.8, 48.6, 22.9, 21.0, 20.93, 20.86, 20.8, 15.18, 15.16. IR: (cm^{-1}) 2361, 2337, 1749, 1685, 1652, 1538, 1441, 1373, 1219. ESIMS *m*/*z* calcd for $C_{25}H_{36}N_4NaO_{12}$ $[M+Na]^+$: 607.22, found: 607.26.

4.5. 5-Acetylamino-4-[4-(1-hydroxy-1-methyl-ethyl)-[1,2,3]triazol-1-yl]-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (11)

5-Acetylamino-4-azido-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester **7** (50 mg, 0.11 mmol) and 2-methyl-but-3-yn-2-ol (15 μL, 0.14 mmol) were dissolved in 2 mL 1:1 mixture of H_2O and *tert*-butyl alcohol. Copper(II) sulfate pentahydrate (1.5 mg, 7.6 μmol) was added, followed by sodium ascorbate (0.04 mL of freshly prepared 1 M solution in water). The mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% NH_4OH followed by brine. Concentration afforded crude product. Further purification was performed by silica gel chromatography (1:3 acetone–toluene), giving compound **11** (80%). TLC (1:3 acetone–toluene): $R_f = 0.32$. ^1H NMR (400 MHz, $CDCl_3$, major rotamer) δ 7.62 (1H, s, triazole), 6.01 (1H, d, $J = 2.4$ Hz, H-3), 5.68 (1H, dd, $J = 2.4$, 10.0 Hz, H-4), 5.56 (1H, dd, $J = 2.0$, 5.6 Hz, H-6), 5.39 (1H, m, H-5), 4.77 (1H, dd, $J = 2.4$, 5.6 Hz, H-7), 4.72 (1H, dd, $J = 1.6$, 10.4 Hz, H-9), 4.40 (1H, dd, $J = 9.6$, 10.4 Hz, H-9′), 4.14 (1H, m, H-8), 3.99 (1H, s, OH), 3.80 (3H, s, OCH_3), 2.07 (3H, s, OAc), 2.04 (3H, s, OAc), 2.01 (3H, s, OAc), 1.73 (3H, s, NAc), 1.56 (3H, s, CH_3), 1.54 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, all rotamers) δ 171.1, 171.0, 170.6, 170.1, 161.5, 156.1, 145.9, 129.1, 128.3, 125.3, 118.8, 107.6, 71.4, 68.1, 67.9, 62.4, 58.6, 52.8, 47.8, 30.5, 30.3, 22.7, 21.0, 20.9, 20.8. IR: (cm^{-1}) 1745, 1658, 1538, 1436, 1371, 1220. ESIMS *m*/*z* calcd for $C_{23}H_{32}N_4NaO_{11}$ $[M+Na]^+$: 563.20, found: 563.34.

4.6. 5-Acetylamino-4-[4-(3-hydroxy-propyl)-[1,2,3]triazol-1-yl]-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (12)

5-Acetylamino-4-azido-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester **7** (50 mg, 0.11 mmol) and pent-4-yn-1-ol (14 μL, 0.14 mmol) were dissolved in 2 mL 1:1 mixture of H_2O and *tert*-butyl alcohol. Copper(II) sulfate pentahydrate (1.5 mg, 7.6 μmol) was added, followed by sodium ascorbate (0.04 mL of freshly prepared 1 M solution in water). The mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% NH_4OH followed by brine. Concentration afforded crude product. Further purification was performed by silica gel chromatography (1:3 acetone–toluene), giving compound **12** (82%). TLC (1:3 acetone–toluene): $R_f = 0.35$. ^1H NMR (400 MHz, $CDCl_3$, major rotamer) δ 7.49 (1H, s, triazole), 7.40 (1H, NH), 6.02 (1H, d, $J = 2.4$ Hz, H-3), 5.69 (1H, dd, $J = 2.4$, 10.0 Hz, H-4), 5.56 (1H, dd, $J = 2.0$, 5.6 Hz, H-6), 5.39–5.42 (1H, m, H-5), 4.77 (1H, dd, $J = 2.8$ Hz, 5.6 Hz, H-7), 4.70 (1H, dd, $J = 1.6$, 10.4 Hz, H-9), 4.39 (1H, dd, $J = 9.6$, 10.4 Hz, H-9′), 4.16 (1H, m, H-8), 3.81 (3H, s, OCH_3), 3.61 (2H, m, CH_2), 2.78 (2H, t, $J = 7.2$ Hz, OCH_2), 2.71 (1H, br s, OH), 2.07 (3H, s, OAc), 2.05 (3H, s, OAc), 2.05 (3H, s, OAc), 1.89 (2H, t, $J = 6.8$ Hz, CH_2), 1.76 (3H, s, NAc). ^{13}C NMR (100 MHz, $CDCl_3$, all rotamer) δ 171.1, 171.0, 170.6, 170.2, 161.5, 148.2, 145.9, 120.3, 107.5, 76.8, 71.3, 67.9, 62.4, 61.3, 58.6, 52.9, 47.9, 31.8, 22.8, 22.1, 21.1, 21.0, 20.8. IR: (cm^{-1}) 1745, 1665, 1547, 1438, 1371, 1220. ESIMS *m*/*z* calcd for $C_{23}H_{32}N_4NaO_{11}$ $[M+Na]^+$: 563.20, found: 563.46.

4.7. 5-Acetylamino-4-{4-[(9*H*-fluoren-9-ylmethoxycarbonylamino)-methyl]-[1,2,3]triazol-1-yl}-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (13)

5-Acetylamino-4-azido-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester **7** (50 mg, 0.11 mmol) and prop-2-ynyl-carbamic acid 9*H*-fluoren-9-ylmethyl ester (40 mg, 0.14 mmol) were dissolved in 2 mL 1:1 mixture of H_2O and *tert*-butyl alcohol. Copper(II) sulfate pentahydrate (1.5 mg, 7.6 μmol) was added, followed by sodium ascorbate (0.04 mL of freshly prepared 1 M solution in water).

The mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% NH_4OH followed by brine. Concentration afforded crude product. Further purification was performed by silica gel chromatography (CH_2Cl_2), giving compound **13** (69%). TLC (CH_2Cl_2): $R_f = 0.20$. ^1H NMR (400 MHz, DMSO-d_6, major rotamer) δ 7.82 (1H, s, triazole), 7.77 (1H, d, $J = 7.2$ Hz, NH), 7.62 (2H, dd, $J = 2.4$, 7.2 Hz), 7.13–7.39 (6H, m), 6.06 (1H, d, $J = 2.0$ Hz, H-3), 5.54 (1H, dd, $J = 2.0$, 6.3 Hz, H-4), 5.50 (1H, dd, $J = 2.0$, 6.3 Hz, H-6), 5.38 (1H, m, H-5), 4.86 (2H, s, CH_2NH), 4.60–4.63 (2H, m, H-8, H-9), 4.34–4.41 (3H, m, OCH_2, CH), 4.14–4.20 (2H, m, H-9′, H7), 3.77 (3H, s, OCH_3), 2.04 (3H, s, OAc), 2.02 (3H, s, OAc), 2.01 (3H, s, OAc), 1.76 (3H, s, NAc). ^{13}C NMR (100 MHz, DMSO-d_6, all rotamers) δ 171.9, 171.2, 170.3, 170.2, 161.7, 146.1, 144.2, 144.1, 141.4, 128.8, 128.1, 127.6, 127.0, 125.2, 125.03, 125.00, 121.7, 119.8, 107.1, 76.7, 70.5, 67.6, 66.6, 62.0, 59.5, 52.0, 36.0, 21.4, 19.7, 19.63, 19.60, 19.5. IR (cm^{-1}): 1743, 1533, 1444, 1371, 1250, 1222. ESIMS m/z calcd for $C_{36}H_{39}N_5NaO_{12}$ $[M+Na]^+$: 756.25, found: 756.34.

4.8. 5-Acetylamino-4-(4-benzoylaminocarbonyl-[1,2,3]triazol-1-yl)-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (14)

5-Acetylamino-4-azido-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester **7** (50 mg, 0.11 mmol) and propynoic acid benzylamide (23 mg, 0.14 mmol) were dissolved in 2 mL 1:1 mixture of H_2O and *tert*-butyl alcohol. Copper(II) sulfate pentahydrate (1.5 mg, 7.6 μmol) was added, followed by sodium ascorbate (0.04 mL of freshly prepared 1 M solution in water). The mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% NH_4OH followed by brine. Concentration afforded crude product. Further purification was performed by silica gel chromatography (EtOAc), giving compound **14** (81%). TLC (EtOAc): $R_f = 0.28$. ^1H NMR (400 MHz, $CDCl_3$, major rotamer) δ 8.43 (1H, s, triazole), 7.74 (1H, t, $J = 6.0$ Hz, NH), 7.21–7.34 (5H, m, Bn), 6.96 (1H, br, NH), 5.97 (1H, d, $J = 2.0$ Hz, H-3), 5.76 (1H, m, H-4), 5.48 (1H, d, $J = 5.6$ Hz, H-6), 5.33 (1H, m, H-5), 4.56–4.72 (4H, m, CH_2, H-8, H-9), 4.24 (1H, dd, $J = 10.0$, 20.0 Hz, H-9′), 4.12 (1H, m, H-8), 3.76 (3H, s, OAc), 2.03 (6H, s, OAc), 1.95 (3H, s, OAc), 1.73 (3H, s, NAc). ^{13}C NMR (100 MHz, $CDCl_3$, all rotamer) δ 170.81, 170.78, 170.4, 170.3, 161.4, 160.0, 146.6, 143.5, 138.0, 128.8, 127.9, 127.7, 125.0, 106.2, 76.7, 71.1, 67.8, 62.2, 58.7, 52.9, 48.7, 43.3, 22.9, 21.0, 20.9, 20.7. IR: (cm^{-1}) 1757, 1662, 1575, 1512, 1438, 1371, 1249, 1222. ESIMS m/z calcd for $C_{28}H_{33}N_5NaO_{11}$ $[M+Na]^+$: 638.21, found: 638.34.

4.9. 2,4,6-Tris-2-yloxymethyl-{5-acetylamino-6-(1,2,3-triacetoxy-propyl)-4-[1,2,3]-2-yloxymethyl-1-yl-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester}-[1,3,5]triazine (15)

5-Acetylamino-4-azido-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester **7** (50 mg, 0.11 mmol) and 2,4,6-tris-prop-2-ynyloxy-[1,3,5]triazine[8] (8.8 mg, 0.03 mmol) were dissolved in 2 mL 1:1 mixture of H_2O and *tert*-butyl alcohol. Copper(II) sulfate pentahydrate (1.5 mg, 7.6 μmol) was added, followed by sodium ascorbate (0.04 mL of freshly prepared 1 M solution in water). The mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% NH_4OH followed by brine. Concentration afforded crude product. Further purification was performed by silica gel chromatography (1:10 MeOH–CH_2Cl_2), giving compound **15** (87%). TLC (1:10 MeOH–CH_2Cl_2): $R_f = 0.38$. ^1H NMR (400 MHz, CD_3OD, major rotamer) δ 8.29 (3H, s, triazole), 6.11 (3H, d, $J = 2.0$ Hz, H-3), 5.64 (3H, m, H-4), 5.51–5.55 (9H, m, CH_2, H-6), 5.45 (3H, m, H-5), 4.69 (3H, m, H-7), 4.56 (3H, dd, $J = 2.4$, 12.4 Hz, H-9), 4.43 (3H, dd, $J = 9.6$, 12.4 Hz, H-9′), 4.14 (3H, m, H-8), 3.79 (9H, s, OCH_3), 2.06 (9H, s, OAc), 2.03 (9H, s, OAc), 2.01 (9H, s, OAc), 1.74 (9H, s, NAc). ^{13}C NMR (100 MHz, CD_3OD, all rotamers) δ 174.0, 172.9, 172.4, 171.7, 171.5, 171.4, 162.9, 147.0, 125,8, 108.5, 95.7, 77.7, 77.4, 71.2, 68.6, 63.2, 62.1, 60.7, 60.4, 57.0, 53.2, 22.6, 20.84, 20.82, 20.7. IR: (cm^{-1}) 2361, 2337, 1745, 1678, 1560, 1417, 1369, 1220. ESIMS m/z calcd for $C_{66}H_{81}N1_5NaO_{33}$ $[M+Na]^+$: 1633.50, found: 1633.41.

4.10. 2,4,6-Tris-2-yloxymethyl-{5-acetylamino-6-(1,2,3-triacetoxy-propyl)-4-[1,2,3]-2-yloxymethyl-1-yl-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester}-[1,3,5]-benzene (16)

5-Acetylamino-4-azido-6-(1,2,3-triacetoxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester **7** (50 mg, 0.109 mmol) and 1,3,5-tris-prop-2-ynyloxy-benzene[8] (8.2 mg, 0.032 mmol) were dissolved in 2 mL 1:1 mixture of H_2O and *tert*-butyl alcohol. Copper(II) sulfate pentahydrate (1.5 mg, 7.57 μmol) was added, followed by sodium ascorbate (0.04 mmol, 0.04 mL of freshly prepared 1 M solution in water). The mixture was stirred at room temperature for 17 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% NH_4OH followed by brine. Concentration afforded crude product. Further purification was performed by silica gel chromatography (1:10 MeOH–CH_2Cl_2), giving compound **16** (85%). TLC (1:10 MeOH–CH_2Cl_2): $R_f = 0.42$. ^1H NMR (400 MHz, CD_3OD, major rotamer) δ 8.14 (3H, s, triazole), 6.27 (3H, s, Ar), 6.10 (3H, d, $J = 2.4$ Hz, H-3), 5.53 (6H, m, H-4, H-5), 5.38

(3H, m, H-6), 5.09 (6H, s, CH_2), 4.62 (6H, m, H-7, H-9), 4.43 (3H, m, H-9′), 4.16 (3H, dd, $J = 6.0$, 12.4 Hz, H-8) 3.81 (9H, s, OCH_3), 2.06 (9H, s, OAc), 2.05 (9H, s, OAc), 2.03 (9H, s, OAc), 1.76 (9H, s, NAc). ^{13}C NMR (100 MHz, CD_3OD, all rotamers) δ 173.1, 172.4, 171.51, 171.46, 162.9, 161.6, 147.3, 145.2, 124.4, 108.4, 96.2, 77.9, 71.6, 68.7, 63.2, 62.5, 60.8, 53.2, 22.6, 20.8, 20.7. ESIMS m/z calcd for $C_{69}H_{81}N_{12}NaO_{33}$ $[M+Na]^+$: 1631.50, found: 1631.91.

4.11. General procedure for compounds 17–25

Compounds **8**–**16** were treated with NaOMe in MeOH at room temperature overnight, then the solvent was evaporated and 1 M NaOH was added. The solution was stirred at room temperature for 2.5 h, then acidified with DOWEX-H 50 resin and filtered. The filtrate was freeze-dried and the products were further purified with p-2 gel, giving **17**–**25**.

4.12. 5-Acetylamino-4-[4-(3-chloro-propyl)-[1,2,3]triazol-1-yl]-6-(1,2,3-trihydroxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid (17)

TLC (1:4 H_2O–2-propanol): $R_f = 0.56$. Yield 72%. ^1H NMR (400 MHz, D_2O, major rotamer) δ 7.89 (1H, s, triazole), 5.14 (1H, d, $J = 1.2$ Hz, H-3), 5.44 (1H, dd, $J = 1.2$, 10.2 Hz, H-4), 4.52 (1H, d, $J = 11.0$ Hz, H-6), 4.33 (1H, dd, $J = 10.2$, 11.0 Hz, H-5), 3.98 (1H, m, H-8), 3.88 (1H, dd, $J = 2.4$, 11.6 Hz, H-9), 3.53–3.69 (4H, m, CH_2Cl, H-9′, H-7), 2.86 (2H, t, $J = 7.2$ Hz, CH_2), 2.08 (2H, q, $J = 6.4$ Hz, CH_2), 1.88 (3H, s, NAc). ^{13}C NMR (100 MHz, D_2O, all rotamers) δ 173.7, 169.0, 155.4, 150.5, 122.2, 120.2, 102.1, 99.4, 75.5, 71.3, 70.0, 69.9, 68.4, 68.2, 63.2, 60.1, 53.9, 48.9, 46.9, 29.1, 29.1, 21.8. ESIMS m/z calcd for $C_{16}H_{23}ClN_4NaO_7$ $[M+Na]^+$: 441.11, found: 441.25.

4.13. 5-Acetylamino-4-(4-propyl-[1,2,3]triazol-1-yl)-6-(1,2,3-trihydroxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid (18)

TLC (1:4 H_2O–2-propanol): $R_f = 0.56$. Yield 81%. ^1H NMR (400 MHz, D_2O, major rotamer) δ 7.83 (1H, s, triazole), 5.81 (1H, d, $J = 2.0$ Hz, H-3), 5.43 (1H, m, H-4), 4.52 (1H, d, $J = 11.0$ Hz, H-6), 4.34 (1H, dd, $J = 9.6$, 11.0 Hz, H-5), 3.97 (1H, m, H-8), 3.88 (1H, dd, $J = 2.4$, 12.0 Hz, H-9), 3.57–3.68 (2H, m, H-9′, H-7), 2.64 (2H, t, $J = 7.2$ Hz, CH_2) 1.87 (3H, s, NAc), 1.62 (2H, q, $J = 7.2$ Hz), 0.85 (3H, m, CH_3). ^{13}C NMR (100 MHz, D_2O, all rotamers) δ 173.6, 168.9, 150.3, 121.7, 102.3, 99.7, 75.5, 71.3, 70.0, 69.9, 68.2, 63.2, 59.9, 53.7, 48.8, 46.9, 26.7, 26.6, 22.2, 21.8, 21.7, 12.9, 12.8. ESIMS m/z calcd for $C_{16}H_{23}ClN_4NaO_7$ $[M+Na]^+$: 407.15, found: 407.48.

4.14. 5-Acetylamino-4-(4-formyl-[1,2,3]triazol-1-yl)-6-(1,2,3-trihydroxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid (19)

TLC (1:4 H_2O–2-propanol): $R_f = 0.43$. Yield 71%. ^1H NMR (400 MHz, D_2O) δ 9.96 (d, $J = 6.0$ Hz, CHO), 8.78 (1H, s, triazole), 5.84 (1H, d, $J = 2.0$ Hz, H-3), 5.57 (1H, m, H-4), 4.40 (1H, $J = 4.0$, 10.4 Hz, H-6), 4.55 (1H, m, H-5), 3.99 (1H, m, H-8) 3.89 (1H, dd, $J = 2.8$, 12.0 Hz, H-9), 3.56–3.70 (2H, m, H-9′, H-8), 1.90 (3H, s, NAc). ^{13}C NMR (100 MHz, D_2O) δ 186.3, 173.9, 169.0, 150.5, 146.7, 128.4, 102.1, 75.5, 69.9, 63.2, 60.6, 54.7, 48.9, 21.8. ESIMS m/z calcd for $C_{14}H_{18}N_4Na_2O_8$ $[M+2Na]^+$: 415.08, found: 415.34.

4.15. 5-Acetylamino-4-[4-(1-hydroxy-1-methyl-ethyl)-[1,2,3]triazol-1-yl]-6-(1,2,3-trihydroxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid (20)

TLC (1:4 H_2O–2-propanol): $R_f = 0.50$. Yield 75%. ^1H NMR (400 MHz, D_2O, major rotamer) δ 7.99 (1H, s, triazole), 5.81 (1H, d, $J = 2.0$ Hz, H-3), 5.47 (1H, dd, $J = 2.0$, 9.6 Hz, H-4), 4.53 (1H, m, H-6), 4.33 (1H, dd, $J = 9.6$, 10.8 Hz, H-5), 3.98 (1H, m, H-8), 3.88 (1H, $J = 2.8$, 12.0 Hz, H-9), 3.56–3.69 (2H, m, H-9′, H-7), 1.88 (3H, s, NAc), 1.58 (3H, s, CH_3). ^{13}C NMR (100 MHz, D_2O, all rotamers) δ 173.6, 169.0, 150.4, 147.4, 122.1, 102.2, 75.5, 69.9, 68.4, 68.2, 63.2, 60.0, 53.9, 48.8, 44.3, 31.5, 31.4, 21.9. ESIMS m/z calcd for $C_{16}H_{24}N_4NaO_8$ $[M+Na]^+$: 423.15, found: 423.28.

4.16. 5-Acetylamino-4-[4-(3-hydroxy-propyl)-[1,2,3]triazol-1-yl]-6-(1,2,3-trihydroxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid (21)

TLC (1:4 H_2O–2-propanol): $R_f = 0.36$. Yield 66%. ^1H NMR (400 MHz, D_2O, major rotamer) δ 7.86 (1H, s, triazole), 5.80 (1H, d, $J = 2.0$ Hz, H-3), 5.44 (1H, m, H-4), 4.52 (1H, m, H-6), 4.33 (1H, dd, $J = 10.0$, 10.8 Hz, H-5), 3.98 (1H, m, H-8), 3.88 (1H, dd, $J = 2.4$, 11.6 Hz, H-9), 3.56–3.68 (4H, m, CH_2, H-9′, H-7), 2.74 (2H, q, $J = 7.6$ Hz, OCH_2), 1.88 (3H, s, NAc), 1.86 (2H, m, CH_2), ^{13}C NMR (100 MHz, D_2O, all rotamers) δ 174.2, 173.6, 169.0, 151.2, 150.4, 148.3, 123.7, 121.7, 102.2, 99.5, 75.5, 71.3, 70.0, 69.9, 68.4, 68.2, 63.2, 60.9, 60.8 59.9, 53.8, 48.8, 46.8, 31.1, 21.8, 21.2. ESIMS m/z calcd for $C_{16}H_{24}N_4NaO_8$ $[M+Na]^+$: 423.15, found: 423.76.

4.17. 5-Acetylamino-4-(4-aminomethyl-[1,2,3]triazol-1-yl)-6-(1,2,3-trihydroxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid (22)

TLC (1:4 H_2O–2-propanol): $R_f = 0.18$. Yield 75%. ^1H NMR (400 MHz, D_2O, major rotamer) δ 8.18 (1H, s, triazole), 5.81 (1H, d, $J = 2.0$ Hz, H-3), 5.54 (1H, m,

H-4), 4.54 (1H, d, $J = 11.2$ Hz, H-6), 4.37 (1H, m, H-5), 4.28 (2H, s, CH_2NH_2), 3.97 (1H, m, H-8), 3.88 (1H, dd, $J = 2.8$, 12.0 Hz, H-9), 3.57–3.69 (2H, m, H-9′, H-7), 1.88 (3H, s, NAc). ^{13}C NMR (100 MHz, D_2O, all rotamers) δ 174.3, 173.9, 168.9, 151.4, 150.6, 147.4, 146.8, 124.7, 122.6, 103.1, 99.4, 76.8, 75.5, 72.4, 71.2, 70.0, 69.9, 68.9, 68.4, 68.2, 63.2, 62.3, 60.0, 55.3, 54.8, 54.7, 54.0, 48.9, 46.8, 21.9, 21.7. Low-resolution ESIMS m/z calcd for $C_{14}H_{21}N_5NaO_7$ $[M+Na]^+$: 394.13, found: 394.51.

4.18. 5-Acetylamino-4-(4-benzylcarbamoyl-[1,2,3]triazol-1-yl)-6-(1,2,3-trihydroxy-propyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid (23)

TLC (1:4 H_2O–2-propanol): $R_f = 0.60$. Yield 62%. ^1H NMR (400 MHz, D_2O) δ 8.49 (1H, s, triazole), 7.38 (5H, m, Bn), 5.84 (1H, d, $J = 2.4$ Hz, H-3), 5.46–5.60 (1H, m, H-4), 4.58 (2H, s, CH_2), 4.40 (1H, m, H-6), 4.33 (1H, dd, $J = 7.2$, 10.8 Hz, H-5), 3.98 (1H, m, H-8), 3.89 (1H, dd, $J = 2.4$, 12.4 Hz, H-9), 3.57–3.69 (2H, m, H-9′, H-7), 1.89 (3H, s, NAc). ^{13}C NMR (100 MHz, D_2O) δ 174.3, 173.7, 168.8, 162.0, 150.7, 150.5, 142.4, 137.9, 128.9, 127.6, 127.4, 126.2, 125.8, 120.2, 102.1, 101.7, 75.5, 71.2, 71.1, 69.9, 69.4, 68.4, 68.2, 63.2, 60.5, 60.0, 54.5, 48.8, 46.7, 43.0, 29.1, 29.0, 21.8, 21.7. ESIMS m/z calcd for $C_{21}H_{25}N_5NaO_8$ $[M+Na]^+$: 498.16, found: 498.40.

4.19. 2,4,6-Tris-2-yloxymethyl-{5-acetylamino-6-(1,2,3-trihydroxy-propyl)-2-yloxymethyl-1-yl-5,6-dihydro-4*H*-pyran-2-carboxylic acid}-[1,3,5]triazine (24)

TLC (1:4 H_2O–2-propanol): $R_f = 0.46$. Yield 69%. ^1H NMR (400 MHz, D_2O, major rotamer) δ 7.90 (3H, s, triazole), 5.68 (3H, d, $J = 2.0$ Hz, H-3), 5.36 (3H, dd, $J = 2.0$, 9.6 Hz, H-4), 4.70 (6H, s, CH_2), 4.55 (3H, m, H-6), 4.01–4.40 (3H, m, H-5), 3.97–4.01 (3H, m, H-8), 3.91 (3H, dd, $J = 2.4$, 11.6 Hz, H-9), 3.57–3.70 (6H, m, H-9′, H-7), 1.89 (9H, s, NAc). ^{13}C NMR (100 MHz, D_2O, all rotamers) δ 174.3, 173.9, 169.0, 151.4, 150.6, 147.4, 146.8, 124.7, 122.6, 102.1, 99.4, 76.8, 75.5, 72.4, 71.2, 70.0, 69.9, 68.9, 68.2, 63.2, 62.3, 60.0, 55.3, 54.8, 54.7, 54.0, 48.8, 46.8, 21.9, 21.7. ESIMS m/z calcd for $C_{42}H_{48}N_{18}O_{24}$ $[M]^{3+}$: 1185.37, found: 1185.60.

4.20. 2,4,6-Tris-2-yloxymethyl-{5-acetylamino-6-(1,2,3-trihydroxy-propyl)-2-yloxymethyl-1-yl-5,6-dihydro-4*H*-pyran-2-carboxylic acid}-[1,3,5]benzene (25)

TLC (1:4 H_2O–2-propanol): $R_f = 0.32$. Yield 69%. ^1H NMR (400 MHz, D_2O, major rotamer) δ 8.15 (3H, s, triazole), 6.36 (3H, s, Bz), 6.85 (3H, d, $J = 2.0$ Hz, H-3), 5.52 (3H, m, H-4), 5.19 (6H, s, CH_2), 4.53 (3H, m, H-6), 4.36 (3H, m, H-5), 3.96 (3H, m, H-8), 3.87 (3H, dd, $J = 2.0$, 12.0 Hz, H-9), 3.56–3.66 (6H, m, H-9′, H-7), 1.78 (9H, s, NAc). ^{13}C NMR (100 MHz, D_2O, all rotamers) δ 174.2, 173.7, 168.5, 159.5, 124.2, 102.5, 99.6, 96.3, 75.6, 71.3, 69.9, 68.3, 68.2, 63.2, 61.4, 60.0, 54.1, 48.8, 46.8, 21.7, 21.6. ESIMS m/z calcd for $C_{45}H_{51}N_{15}NaO_{24}$ $[M+Na]^+$: 1211.37, found: 1211.8.

4.21. 2-[2-(2-Azido-ethoxy)-ethoxy]-ethylamine

2-[2-(2-Amino-ethoxy)-ethoxy]-ethylamine (2.0 g, 13.5 mmol) and DISEA (1.6 mL, 12.52 mmol) were dissolved in 50 mL THF and stirred vigorously in room temperature. Di-*tert*-butyl dicarbonate (1.23 g, 5.67 mmol) was dissolved in 200 mL THF and added dropwise to amine solution. The mixture was stirred in room temperature for 24 h. The solvent was evaporated. The reaction mixture was dissolved in EtOAc and washed with satd aq $NaHCO_3$. Concentration afforded 1.0 g crude product as yellowish oil, then dissolved in 9 mL water and 18 mL MeOH, TfN_3 (5 mL of freshly prepared 1.6 M solution in CH_2Cl_2) was stirred at room temperature for 18 h. The reaction mixture was dissolved in EtOAc, washed with satd aq $NaHCO_3$ and brine. Concentration afforded crude product as yellowish oil, then further purified by silica gel chromatography (1:4 EtOAc–hexane), giving {2-[2-(2-azido-ethoxy)-ethoxy]-ethyl}-carbamic acid *tert*-butyl ester 1.16 g (yield 74.6%). TLC (1:4 EtOAc–hexane): $R_f = 0.33$. ^1H NMR (400 MHz, $CDCl_3$) δ 3.45–3.54 (6H, m), 3.38 (2H, t, $J = 7.2$ Hz), 3.24 (2H, t, $J = 6.8$ Hz), 3.14 (2H, m), 1.28 (9H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 78.7, 70.2, 70.0, 69.9, 69.8, 50.3, 40.0, 28.1. Deprotection of the Boc protection group was carried out on using 20% TFA in CH_2Cl_2 (5 mL) for 2.5 h. The solvent was evaporated and the reaction mixture was dissolved in EtOAc, washed with satd aq $NaHCO_3$. Concentration afforded crude product as a yellowish oil, which was further purified by silica gel chromatography (1:10:0.3 MeOH–CH_2Cl_2–TEA), giving azide 0.46 g (yield 56%). TLC (1:10:0.3 MeOH–CH_2Cl_2–TEA): $R_f = 0.20$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.51 (2H, br s), 3.57–3.63 (8H, m), 3.36 (2H, t, $J = 4.8$ Hz), 3.01 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.4, 70.2, 69.9, 69.8, 50.6, 40.1. ESIMS m/z calcd for $C_6H_{15}N_4O_2$ $[M+H]^+$: 175.11, found: 175.12.

4.22. 5-Acetylamino-6-[{2-[2-(2-azido-ethoxy)-ethoxy]-ethylcarbamoyloxy}-(2,2-dimethyl-[1,3]dioxolan-4-yl)-methyl]-4-(2-*tert*-butoxycarbonylamino-2-*tert*-butoxycarbonylimino-ethyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (30)

The linker (46.3 mg, 0.266 mmol) and DMAP (32 mg, 0.266 mmol) was added to a solution of **29** (100 mg, 0.133 mmol) in 2 mL dry pyridine. The reaction mixture was stirred vigorously for 2 days at room temperature.

The solution was then concentrated and the residue was extracted with EtOAc and purified by column chromatography (1:1 hexane–EtOAc) to give **30** (87 mg, 83%). TLC (1:1 hexane–EtOAc): $R_f = 0.34$. ^{1}H NMR (400 MHz, $CDCl_3$, major rotamer) δ 11.39 (1H, s, NH), 8.44 (1H, d, $J = 8.4$ Hz, NH), 6.08 (1H, d, $J = 8.8$ Hz, NH), 5.87 (1H, d, $J = 2.0$ Hz, H-3), 5.34 (1H, m, H-7), 5.17–5.24 (2H, m, H-4, H-6), 4.36 (2H, d, $J = 8.4$ Hz, CH_2), 4.05–4.13 (3H, m, H-5, H-8, H-9), 4.02 (1H, m, H-9′), 3.78 (3H, s, OCH_3), 3.52–3.68 (8H, m), 3.34–3.40 (4H, m), 1.92 (3H, s, NAc), 1.47 (18H, s, Boc), 1.38 (3H, s, CH_3), 1.34 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, all rotamers) δ 170.9, 163.2, 162.1, 157.1, 155.7, 152.9, 145.4, 115.9, 109.9, 83.8, 79.8, 77.6, 74.7, 70.7, 70.4, 70.1, 70.0, 69.9, 52.6, 50.8, 48.9, 48.5, 41.2, 28.4, 28.2, 26.7, 25.6, 23.3. ESIMS m/z calcd for $C_{33}H_{54}N_8NaO_{14}$ $[M+Na]^+$: 809.37, found: 809.30.

4.23. 2,4,6-Tris-2-yloxymethyl-{5-acetylamino-6-[{2-[2-(2-[1,2,3]triazol-ethoxy)-ethoxy]-ethylcarbamoyloxy}-(2,2-dimethyl-[1,3]dioxolan-4-yl)-methyl]-4-(2-*tert*-butoxycarbonylamino-2-*tert*-butoxycarbonylimino-ethyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester}-[1,3,5]triazine (31)

Azide **30** (81.7 mg, 0.10 mmol) and 2,4,6-tris-prop-2-ynyloxy-[1,3,5]triazine[8] (8.4 mg, 0.035 mmol) were dissolved in 2 mL 1:1 mixture of H_2O and *tert*-butyl alcohol. Copper(II) sulfate pentahydrate (1.5 mg, 7.57 μmol) was added, followed by sodium ascorbate (0.04 mL of freshly prepared 1 M solution in water). The mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% NH_4OH followed by brine. Concentration afforded crude product. Further purification was performed by silica gel chromatography (1:10 MeOH–EtOAc), giving compound **31** (69%). TLC (1:10 MeOH–EtOAc): $R_f = 0.26$. ^{1}H NMR (400 MHz, $CDCl_3$, major rotamer) δ 11.37 (3H, s, NH), 8.49 (3H, d, $J = 8.4$ Hz, NH), 7.95 (3H, s, triazole), 6.43 (3H, d, $J = 8.8$ Hz, NH), 5.86 (3H, d, $J = 2.4$ Hz, H-3), 5.57 (6H, s, CH_2), 5.41 (3H, m, H-7), 5.20 (6H, t, $J = 8.0$ Hz, CH_2), 4.55 (6H, m, H-4, H-6), 4.32–4.40 (6H, m, CH_2), 4.05–4.12 (9H, m, H-5, H-8, H-9), 3.98 (3H, t, $J = 8.8$ Hz, H-9′), 3.86 (6H, t, $J = 4.8$ Hz, CH_2), 3.76 (9H, s, OCH_3), 3.55 (15H, m, CH_2, H-9′), 3.29 (6H, m, CH_2), 1.89 (9H, s, NAc), 1.45 (27H, s, Boc), 1.44 (27H, s, Boc), 1.33 (9H, s, CH_3), 1.31 (9H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, all rotamers) δ 172.8, 171.1, 163.1, 162.1, 157.0, 155.7, 152.8, 145.2, 142.0, 126.2, 125.3, 115.9, 110.1, 109.0, 83.7, 79.7, 74.7, 70.6, 70.2, 69.9, 69.4, 66.0, 61.6, 52.6, 50.4, 49.0, 48.3, 41.0, 28.3, 28.1, 26.6, 25.5, 23.2. ESIMS m/z calcd for $C_{111}H_{171}N_{27}O_{45}$ $[M+2Na]^{2+}$: 2628.17, found: 2628.4.

4.24. 2,4,6-Tris-2-yloxymethyl-{5-acetylamino-6-[{2-[2-(2-[1,2,3]triazol-ethoxy)-ethoxy]-ethylcarbamoyloxy}-(2,2-dimethyl-[1,3]dioxolan-4-yl)-methyl]-4-(2-*tert*-butoxycarbonylamino-2-*tert*-butoxycarbonylimino-ethyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester}-[1,3,5]benzene (32)

Azide **30** (108.7 mg, 0.14 mmol) and 1,3,5-tris-prop-2-ynyloxy-benzene[8] (11.1 mg, 0.046 mmol) were dissolved in 2 mL 1:1 mixture of H_2O and *tert*-butyl alcohol. Copper(II) sulfate pentahydrate (1.5 mg, 7.57 μmol) was added, followed by sodium ascorbate (0.04 mL of freshly prepared 1 M solution in water). The mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% NH_4OH followed by brine. Concentration afforded crude product. Further purification was performed by silica gel chromatography (1:10 MeOH–EtOAc), giving compound **32** (85%). TLC (1:10 MeOH–EtOAc): $R_f = 0.22$. ^{1}H NMR (400 MHz, CD_3OD, major rotamer) δ 8.12 (3H, s, triazole), 8.09 (3H, dd, $J = 2.8$ Hz, NH), 6.88 (3H, t, $J = 5.6$ Hz, NH), 6.35 (3H, s, Bz), 5.92 (3H, d, $J = 2.0$ Hz, H-3), 5.24 (3H, d, $J = 1.2$, 5.6 Hz, H-7), 5.17 (6H, s, CH_2), 4.97 (3H, dd, $J = 2.0$, 10.0 Hz, H-4), 4.61 (6H, t, $J = 5.2$ Hz, CH_2), 4.35 (6H, m, H-6, H-8), 4.07–4.17 (6H, m, H-5, H-9), 3.98 (3H, dd, $J = 6.4$, 8.8 Hz, H-9′), 3.90 (6H, t, $J = 5.2$ Hz, CH_2), 3.76 (9H, s, OCH_3), 3.57–3.62 (12H, m, CH_2), 3.39 (6H, m, CH_2), 3.24 (6H, m, CH_2), 1.89 (9H, s), 1.49 (27H, s), 1.46 (27H, s), 1.34 (9H, s), 1.30 (9H, s). ^{13}C NMR (100 MHz, CD_3OD, all rotamers) δ 173.3, 164.3, 163.4, 161.6, 158.0, 157.6, 153.8, 125.8, 144.7, 126.2, 111.2, 110.1, 96.3, 84.8, 80.5, 78.4, 76.2, 71.4, 71.2, 70.8, 70.3, 66.9, 62.6, 53.0, 51.5, 51.1, 48.0, 41.9, 28.5, 28.3, 26.9, 25.8, 22.8. ESIMS m/z calcd for $C_{116}H_{178}N_{24}Na_2O_{45}$ $[M+2Na]^{2+}$: 2645.19, found: 2645.24.

4.25. 5-Acetylamino-6-[2-{2-[2-(4-ylmethyl-carbamic acid 9*H*-fluoren-9-ylmethyl ester [1,2,3]triazol)-ethoxy]-ethylcarbamoyloxy}-(2,2-dimethyl-[1,3]dioxolan-4-yl)-methyl]-4-(2-*tert*-butoxycarbonylamino-2-*tert*-butoxycarbonylimino-ethyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (33)

Azide **30** (76.4 mg, 0.097 mmol) and prop-2-ynyl-carbamic acid 9*H*-fluoren-9-ylmethyl ester (35 mg, 0.13 mmol) were dissolved in 2 mL 1:1 mixture of H2O and *tert*-butyl alcohol. Copper(II) sulfate pentahydrate (1.5 mg, 7.57 μmol) was added, followed by sodium ascorbate (0.04 mL of freshly prepared 1 M solution in water). The mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% NH_4OH followed by brine. Concentration afforded crude product. Further purification was performed by silica gel chromatography

(1:10 MeOH–CH_2Cl_2), giving compound **33** (87%). TLC (1:10 MeOH–CH_2Cl_2): $R_f = 0.37$. ^{1}H NMR (400 MHz, $CDCl_3$, major rotamer) δ 11.39 (1H, s, NH), 7.73 (3H, m, Ar, triazole), 7.56 (2H, d, $J = 7.2$ Hz, Ar), 7.36 (2H, t, $J = 7.6$ Hz, Ar), 7.26 (2H, $J = 8.0$ Hz, Ar), 6.19 (1H, d, $J = 8.8$ Hz), 5.85 (1H, d, $J = 2.4$ Hz, H-3), 5.44 (1H, m, H-7), 5.29 (1H, s, NH), 5.22 (1H, m, H-4), 4.44–4.50 (5H, m, $2CH_2$, CH), 4.31–4.35 (4H, m, CH_2, H-6, H-8), 4.17 (1H, m, H-5), 4.03–4.12 (1H, m, H-9), 3.98 (1H, m, H-9′), 3.73 (3H, s), 3.56 (4H, m, CH_2), 3.46 (2H, m, CH_2), 3.26 (2H, m, CH_2), 1.88 (3H, s, NAc), 1.44 (9H, s, Boc), 1.43 (9H, s, Boc), 1.33 (3H, s, CH_3), 1.30 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, all rotamers) δ 171.0, 163.1, 162.0, 157.0, 152.8, 145.0, 143.9, 141.3, 127.7, 127.1, 125.2, 123.3, 120.0, 110.1, 109.0, 83.7, 79.7, 74.7, 70.6, 70.1, 69.9, 69.8, 66.9, 66.0, 60.5, 52.5, 50.3, 49.1, 48.1, 47.2, 41.1, 36.6, 28.3, 28.1, 26.6, 25.4, 23.2, 21.1, 14.3. ESIMS *m/z* calcd for $C_{51}H_{69}N_9NaO_{16}$ $[M+Na]^+$: 1086.48, found: 1086.17.

4.26. 1-[2-(2-{2-[(3-Acetylamino-4-(2-*tert*-butoxycarbonylamino-2-*tert*-butoxycarbonylimino-ethyl)-6-methoxycarbonyl-3,4-dihydro-2*H*-pyran-2-yl)-(2,2-dimethyl-[1,3]dioxolan-4-yl)-methoxycarbonylamino]-ethoxy}-ethoxy)-ethyl]-1*H*-[1,2,3]triazole-4-carboxylic acid methyl ester (34)

Azide **30** (48.1 mg, 0.06 mmol) and prop-2-ynylcarbamic acid 9*H*-fluoren-9-ylmethyl ester (7 μL, 0.078 mmol) were dissolved in 2 mL 1:1 mixture of H_2O and *tert*-butyl alcohol. Copper(II) sulfate pentahydrate (1.5 mg, 7.57 μmol) was added, followed by sodium ascorbate (0.04 mL of freshly prepared 1 M solution in water). The mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% NH_4OH followed by brine. Concentration afforded crude product. Further purification was performed by silica gel chromatography (1:10 MeOH–CH_2Cl_2), giving compound **35** (83%). TLC (1:10 MeOH–CH_2Cl_2): $R_f = 0.42$. ^{1}H NMR (400 MHz, $CDCl_3$, major rotamer) δ 11.38 (1H, s, NH), 8.40 (1H, s, triazole), 8.39 (1H, d, $J = 9.2$ Hz, NH), 5.86 (1H, d, $J = 2.0$ Hz, H-3), 5.50 (1H, m, H-7), 5.19 (2H, m, H-4, H-6), 4.60 (2H, t, $J = 4.8$ Hz, CH_2), 4.32 (2H, t, $J = 7.6$ Hz, CH_2), 4.06 (2H, m, H-5, H-8), 3.98 (1H, m, H-9), 3.94 (1H, m, H-9′), 3.93 (3H, s, OCH_3), 3.85 (1H, dd, $J = 5.2$, 10.0 Hz, CH_2), 3.75 (3H, s, OCH_3), 3.49–3.62 (6H, m, $3CH_2$), 3.33 (2H, m, CH_2), 1.89 (3H, s, NAc), 1.50 (9H, s, Boc), 1.45 (9H, s, Boc), 1.36 (3H, s, CH_3), 1.32 (3H, s, CH_3), ^{13}C NMR (100 MHz, $CDCl_3$, all rotamers) δ 170.8, 163.2, 162.0, 161.6, 157.0, 155.7, 152.9, 145.3, 139.9, 129.2, 110.1, 109.9, 109.0, 83.7, 79.7, 74.9, 70.5, 69.9, 69.6, 69.0, 66.0, 65.8, 52.7, 52.2, 50.5, 49.2, 48.8, 48.2, 41.2, 28.4, 28.3, 26.8, 25.6, 23.2. ESIMS *m/z* calcd for $C_{37}H_{58}N_8NaO_{16}$ $[M+Na]^+$: 893.39, found: 893.70.

4.27. General procedure for the preparation of 35–38

Compounds **31**–**34** were treated with 50% TFA–CH_2Cl_2 at room temperature for 2.5 h, then the solvent was evaporated and 1 M NaOH was added. The solution was stirred at room temperature for 0.5 h, then acidified with DOWEX-H 50 resin and filtered. The filtrate was freeze-dried and the products were further purified with p-2 gel, giving **35**–**38**.

4.28. 2,4,6-Tris-2-yloxymethyl-{5-acetylamino-6-[{2-[2-(2-[1,2,3]triazol-ethoxy)-ethoxy]-ethylcarbamoyloxy}-propyl]-4-guanidino-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester}-[1,3,5]triazine (35)

TLC (1:4 H_2O–2-propanol): $R_f = 0.27$. Yield 75%. ^{1}H NMR (400 MHz, CD_3OD, major rotamer) δ 8.21 (3H, s, triazole), 5.87 (3H, s, H-3), 5.60 (6H, s, CH_2), 4.58 (6H, m, CH_2), 4.52 (3H, m, H-7), 4.39 (3H, m, H-4), 4.08 (3H, m, H-6), 3.89 (6H, m, H-5, H-8), 3.76 (12H, m, CH_2, H-9, H-9′), 3.53 (18H, m, CH_2), 3.16 (6H, m, CH_2), 1.82 (9H, s, NAc). ^{13}C NMR (100 MHz, D_2O, all rotamers) δ 174.0, 172.4, 163.5, 157.1, 156.6, 144.5, 142.2, 126.6, 126.2, 109.4, 76.0, 69.7, 69.4, 69.1, 68.9, 68.8, 62.4, 61.2, 53.1, 51.2, 50.3, 47.1, 40.3, 21.9. ESIMS *m/z* calcd for $C_{69}H_{106}N_{27}Na_2O_{33}$ $[M+2Na]^{2+}$: 1883.73, found: 1883.32.

4.29. 2,4,6-Tris-2-yloxymethyl-{5-acetylamino-6-[{2-[2-(2-[1,2,3]triazol-ethoxy)-ethoxy]-ethylcarbamoyloxy}-propyl]-4-guanidino-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester}-[1,3,5]benzene (36)

TLC (1:4 H_2O–2-propanol): $R_f = 0.23$. Yield 80%. ^{1}H NMR (400 MHz, D_2O, major rotamer) δ 8.08 (3H, s, triazole), 6.32 (3H, s, Ar), 5.60 (3H, d, $J = 2.0$ Hz, H-3), 4.58 (6H, t, $J = 4.0$ Hz, CH_2), 4.41 (3H, dd, $J = 2.0$, 9.6 Hz, H-7), 4.28–4.35 (3H, m, H-4), 4.18 (3H, m, H-6), 4.08–4.13 (6H, m, H-5, H-8), 3.90 (9H, t, $J = 4.0$ Hz, CH_2, H-9), 3.69 (3H, d, $J = 9.2$ Hz, H-9′), 3.37–3.49 (24H, m, CH_2), 3.16 (6H, m, CH_2), 1.96 (9H, s, NAc). ^{13}C NMR (100 MHz, D_2O, all rotamers) δ 171.5, 169.4, 162.8, 159.9, 158.6, 156.7, 145.0, 142.4, 125.0, 108.2, 94.5, 76.5, 69.5, 69.4, 69.2, 69.0, 68.7, 68.5, 67.3, 66.7, 61.2, 49.4, 49.3, 47.5, 22.6. ESIMS *m/z* calcd for $C_{72}H_{111}N_{27}O_{33}$ $[M+3H]^{3+}$ 1839.75, found: 1839.39.

4.30. 5-Acetylamino-6-[1-(2-{2-[2-(4-aminomethyl-[1,2,3]triazol-1-yl)-ethoxy]-ethoxy}-ethylcarbamoyloxy)-2,3-dihydroxy-propyl]-4-guanidino-5,6-dihydro-4*H*-pyran-2-carboxylic acid (37)

TLC (1:4 H_2O–2-propanol): $R_f = 0.13$. Yield 60%. ^{1}H NMR (400 MHz, D_2O, major rotamer) δ 7.88 (1H, s, triazole), 5.41 (1H, d, $J = 2.0$ Hz, H-3), 4.44 (1H, m, H-7), 4.25 (1H, dd, $J = 2.0$, 9.2 Hz, H-4), 4.18 (1H, d,

$J = 10.4$ Hz, H-6), 4.03 (2H, t, $J = 10.0$ Hz, CH_2), 3.95 (2H, m, H-5, H-8), 3.73–3.80 (2H, m, CH_2), 3.69 (1H, dd, $J = 2.8$, 12.0 Hz, H-9), 3.52 (1H, d, $J = 8.4$ Hz, H-9′), 3.46 (4H, m, $2CH_2'$), 3.34 (2H, m, CH_2), 3.09 (2H, m, CH_2), 1.83 (3H, s, NAc). ^{13}C NMR (100 MHz, D_2O, all rotamers) δ 174.5, 169.3, 167.6, 157.1, 149.3, 141.8, 127.9, 125.3, 118.6, 104.0, 75.5, 75.3, 69.9, 69.7, 69.4, 68.8, 68.3, 66.5, 63.2, 51.1, 50.2, 47.9, 40.2, 22.1, 22.0. ESIMS *m/z* calcd for $C_{22}H_{38}N_9O_{10}$ $[M+H]^+$: 588.27, found: 588.15.

4.31. 1-[2-(2-{2-[1-(3-Acetylamino-6-carboxy-4-guanidino-3,4-dihydro-2*H*-pyran-2-yl)-2,3-dihydroxy-propoxycarbonylamino]-ethoxy}-ethoxy)-ethyl]-1*H*-[1,2,3]triazole-4-carboxylic acid (38)

TLC (1:4 H_2O–2-propanol): $R_f = 0.20$. Yield 76%. ^{1}H NMR (400 MHz, D_2O, major rotamer) δ 8.29 (1H, s, triazole), 5.60 (1H, d, $J = 2.4$ Hz, H-3), 4.62 (2H, t, $J = 4.4$ Hz, CH_2), 4.43 (1H, d, $J = 8.8$ Hz, H-7), 4.34 (1H, m, H-4), 4.14–4.21 (2H, m, H-6, H-8), 4.08 (1H, m, H-5), 3.95 (2H, t, $J = 4.8$ Hz, CH_2), 3.72 (1H, d, $J = 9.2$ Hz, H-9), 3.54–3.62 (5H, m, $2CH_2$, H-9′), 3.49 (2H, t, $J = 5.2$ Hz, CH_2), 3.24 (2H, t, $J = 4.8$ Hz, CH_2), 1.97 (3H, s). ^{13}C NMR (100 MHz, D_2O, all rotamers) δ 174.5, 169.1, 158.7, 157.1, 149.2, 128.1, 118.6, 104.9, 104.2, 103.9, 75.4, 69.8, 69.4, 68.8, 67.7, 66.2, 63.2, 51.2, 50.3, 47.9, 40.2, 22.1. ESIMS *m/z* calcd for $C_{22}H_{35}N_8O_{12}$ $[M+H]^+$: 603.23, found: 603.18.

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Supplementary data

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