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Synthesis and characterization of pentaerythritol derived glycoconjugates as supramolecular gelators

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Abstract

Carbohydrate based self-assembling supramolecular systems are important classes of new materials with many potential applications In this study, a series of twelve glycoconjugates were synthesized and characterized in order to obtain effective supramolecular gelators. These glycoconjugates are mono-, di-, tri-, and tetra- functionalized pentaerythritol derivatives synthesized by using copper (I) catalyzed azide alkyne cycloaddition reactions (CuAACs). The properties of these twelve compounds gave insight into rational design of covalently linking multiple units of sugars.We found that the trivalent and tetravalent glycoclusters were effective molecular gelators, but the monovalent and divalent derivatives were typically not able to form gels in the tested solvents. The gels were characterized using rheology, optical microscopy, and atomic force microscopy. The tris-triazole derivative **21** was discovered to be a suitable gelator for encapsulation of naproxen, vitamin B_2, and vitamin B_{12}. The strategy of covalently linking three or four small molecules to form trimeric or tetrameric branched compounds is a valid approach in designing useful self-assembling materials. The glycocluster based organogels and hydrogels obtained in this study have potential applications in biomedical research and as advanced functional materials.

Keywords: Self-assembly; Supramolecular gels; Carbohydrates; Glycoclusters; Dendritic gelators

Introduction

In recent years, low molecular weight gelators (LMWGs) have gained much attention as a unique class of compounds.[1-5] LMWGs, also termed supramolecular gelators or molecular gelators, can self-assemble and interact with solvents in a particular manner that result in the formation of reversible gels.[6,7] The main driving forces of the formation of self-assembled supramolecular networks are non-covalent intermolecular interactions such as hydrogen bonding, π-π stacking, CH-π interactions, halogen bonding, hydrophobic effects, and van der Waals forces. The resulting gels are unique soft materials that are useful in biomedical research for drug delivery, enzyme immobilization, and scaffolds for tissue engineering.[4,8,9] Some low molecular weight hydrogelators have shown anticancer properties, along with uses in other biomedical applications through the physical gelation mechanism.[10] LMWGs have been explored for optical electronic applications and as stimuli-responsive advanced functional materials.[5,11-13] Supramolecular gelators have also been used for catalysis[14,15] and environmental applications.[16-20] Although it is still challenging to predict the gelation properties of certain compounds,[21,22] we have shown that it is possible to rationally design sugar based gelators from common templates and functional group manipulations.[23-25]

Carbohydrates are renewable resources with rich structural diversity and chirality. They are useful as starting materials for the preparation of functional glycoconjugates. A variety of glycoconjugates have been synthesized and studied using the copper catalyzed azide alkyne cycloaddition (CuAAC), the "Click" chemistry.[26-28] The biological applications of glycoconjugates have been well studied, but systematic design and application of glycoconjugates for molecular gelators have not been thoroughly studied. Carbohydrate based gelators are likely to

be biocompatible and they may be applicable as advanced materials in different fields. We have been interested in converting simple carbohydrates to molecular gelators that can form functional molecular assemblies with desired properties. In previous studies, we have found that selective functionalization of D-glucose or D-glucosamine at different positions can produce effective molecular gelators.[23,29,30] Several series of LMWGs and functional molecular assemblies have been discovered by introducing a triazole moiety to various sugar molecules. The monomeric glucose and glucosamine triazoles **I** (Figure 1) have been previously studied and we found that only certain triazole derivatives (R = $(CH_2)_{11}OH$ for instance) were able to form gels.[29] These derivatives were effective to solidify alcohols, DMSO and water mixtures, ethanol and water mixtures, and water. The glucosamine derivatives were more effective gelators than the glucose derivatives when R groups are the same. The intermolecular forces contributing to the gelators and molecular self-assemblies are shown in Figure 1.

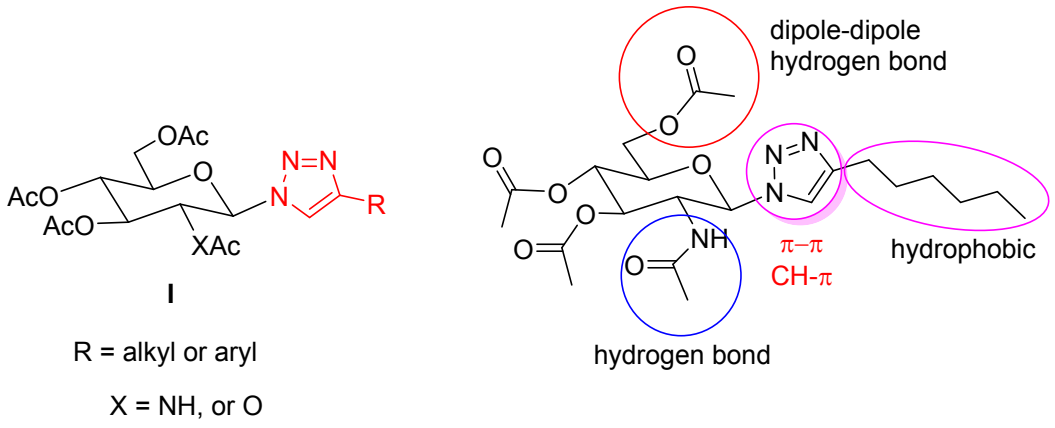


Figure 1. General structure of sugar triazole derivatives **I** and the intermolecular forces of a glucosamine triazole based gelator.

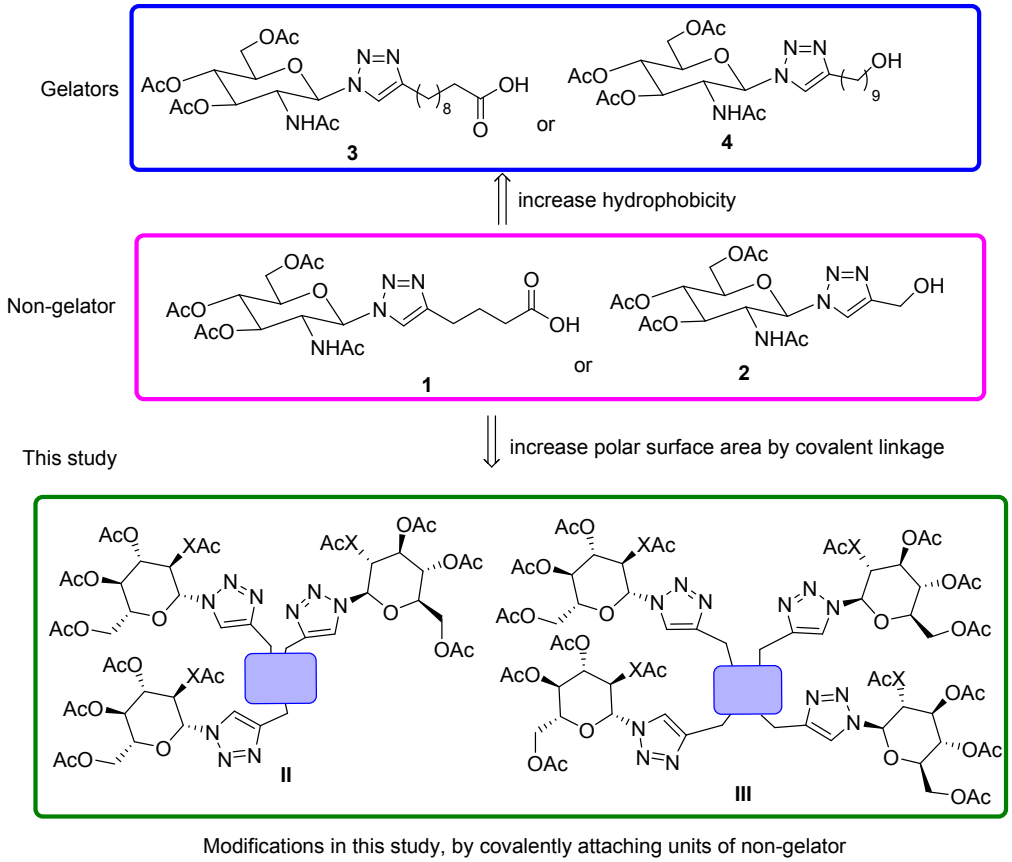


Figure 2. Glucosamine triazole derivatives using different alkynes and the rational design of glycoclusters **II** and **III** for molecular gelators.

The short chain derivatives with carboxylic acid and alcohol such as compounds **1** and **2** were not gelators in any of the tested solvents. To convert a non-gelator to a supramolecular gelator, we can first analyze the effect of changing the R group in **I** to obtain the desirable features. For example, by adding hydrophobic methylene groups to compounds **1** and **2**, forming derivatives **3** and **4**, effective gelators were obtained (Figure 2). An alternative approach to designing effective gelators is to covalently tether several non-gelators to form a small cluster or branched system. This changes and enhances both the intramolecular and intermolecular interactions while still maintaining a simple modular approach. For example, the hydroxyl methyl substituted compound

2 was not a gelator, but covalently tethering three or four of these molecules in a cluster could lead to stronger interactions, which may lead to effective gelators. The design strategy takes the molecular interactions of the individual small molecules into consideration and enhances the interactions through covalently linking them together. Since the supramolecular gel networks are held together solely by weak intermolecular forces, we speculate that by covalently connecting several glycosyl triazole molecules to afford the general structures of **II** and **III**, supramolecular gelators could be obtained. These glycoclusters have similar shapes to dendritic or branched molecules. Dendritic compounds with suitably arranged functional groups and defined structures may lead to effective self-assembling materials, including organogels and hydrogels.[31] These systems have larger molecular weight than previous carbohydrate based gelators, therefore they would be able to interact with large biomolecules more readily through multivalent interactions. In addition, these compounds also have single molecule weight and are expected to behave more like low generation dendrimers, which could lend them to potential applications as effective catalysts or as template for binding with proteins.

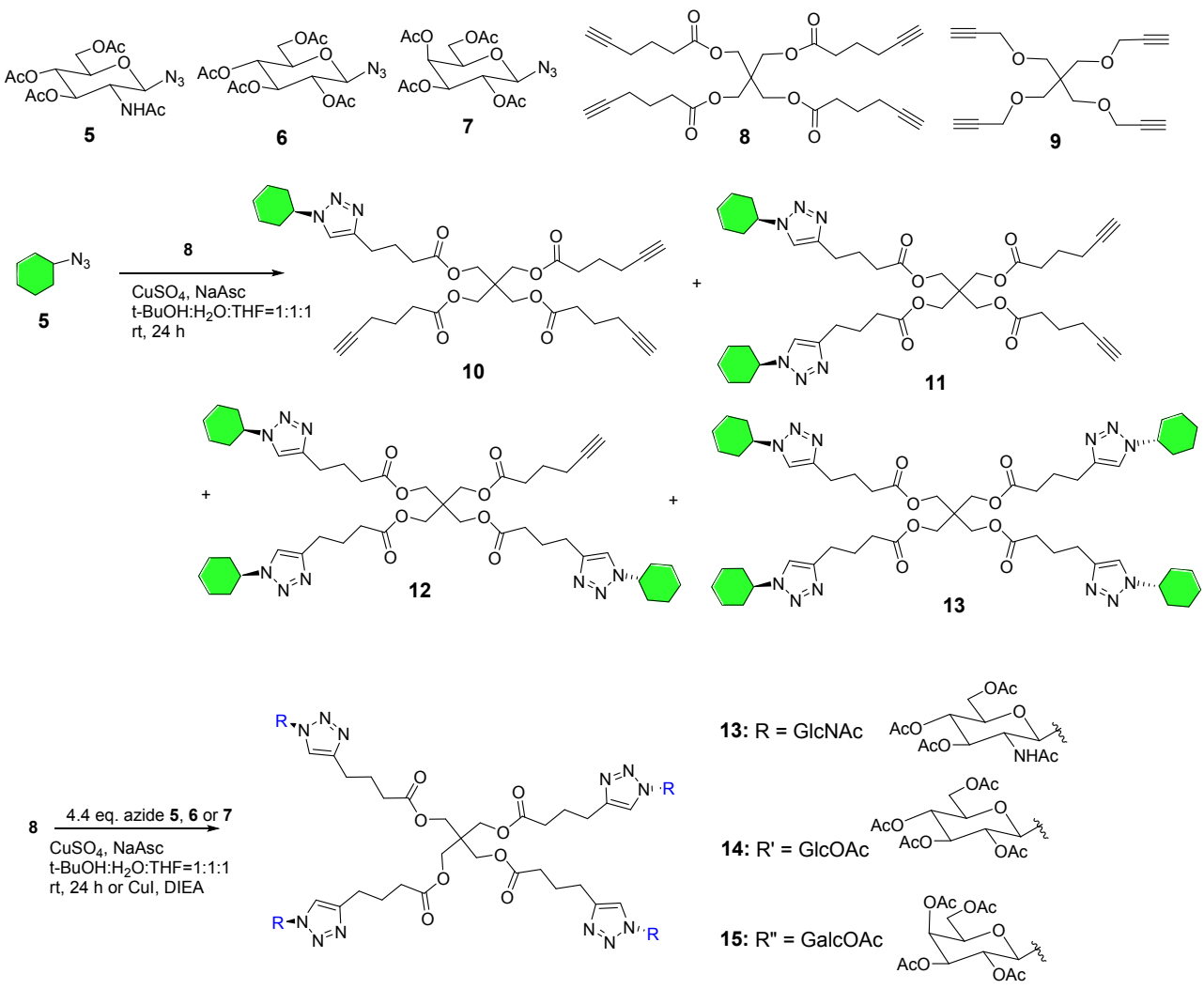
Results and discussions

As shown in Figure 2, we hypothesize that forming glycoclusters by covalently linking several small sugar derivatives can be an effective method to obtain useful molecular assemblies and LMWGs. To test this hypothesis, we used the popular tetra branched pentaerythritol as the building block to synthesize derivatives with different numbers of sugar triazole units. Scheme 1 shows the structures of the building blocks, per-acetylated sugar azide derivatives **5-7**, which were synthesized from glucose, N-acetyl 2-deoxy-2-glucosamine, and galactose, respectively. Using pentaerythritol as the starting material, the tetrameric alkynyl ester **8** was synthesized by

esterification with 5-hexynoyl chloride.[32,33] The tetra alkynyl ether **9** was synthesized by Williamson ether synthesis using sodium hydride and propargyl chloride.[34-37] These tetrameric alkynes were then used in the synthesis of glycoconjugates by click chemistry.

The N-acetyl glucosamine triazole acid analog **1** was found to be a non-gelator in several solvents (SI page S4-S5). In order to study the effect of covalently connecting different numbers of per-acetylated sugars into a cluster, we utilized a one-pot reaction strategy to synthesize derivatives containing different number of sugar triazole chains. Using the tetra alkyne ester **8**, as shown in Scheme 1, we carried out partial click reactions using two equiv. of azide **5** with one equiv. of compound **8** to obtain a mixture of monomeric, dimeric, trimeric, and tetrameric triazole adducts in a one-pot reaction. The four products were then carefully separated using flash chromatography with a gradient of solvent system. These compounds were then tested for gelation properties in a series of solvents starting from 20 mg/mL concentration. These solvents include toluene, a series of alcohols, DMSO and water mixture, ethanol and water mixture, and water. The results are summarized in Table 1. There is an obvious trend that increasing the number of sugar units in the molecules leads to an enhancement of gelation properties. The monomeric and dimeric triazole derivatives **10** and **11** did not form gels in these solvents. The tris-triazole derivative **12** formed gels in ethanol and isopropanol at 20 mg/mL. The tetra-triazole glycoconjugate **13** was the most effective gelator among these four derivatives. It formed stable gels in all five selected alcohols including glycerol and forming a gel in isopropanol at 4.0 mg/mL. These results support our design principles. An increased tendency of gelation was found with an increase in the number of covalently attached peracetylated sugar triazole in each cluster, with the tetrameric glycoconjugates being the most versatile gelators.

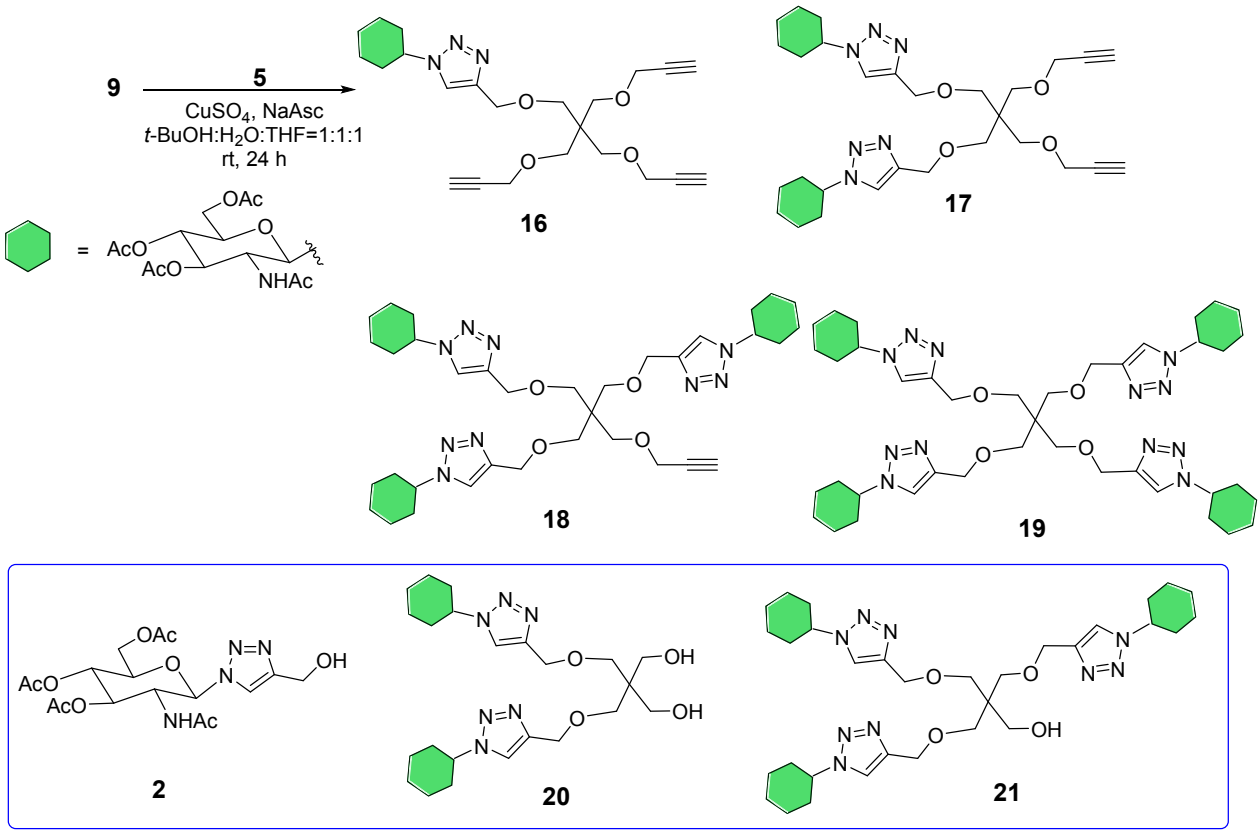
After finding out that the tetrameric click reaction product **13** was the most effective gelator among the four glycoconjugates, we explored the effect of changing the peripheral carbohydrate moieties. Two other tetrameric triazole derivatives with different sugar units at the periphery were synthesized, glucose derivative **14** and galactose derivative **15**. These two compounds were not effective gelators for all tested solvents except glycerol, in which they formed gels at 20 mg/mL. This indicated that in addition to the cluster effect of multiple sugar units, the sugar structures play an important role in the molecular self-assembly and gelation. The glucosamine derivative **13** was the most effective gelator among the three tetramers **13-15**. This result indicates that the amide functional group, which is both a hydrogen bond donor and acceptor, plays a very important role in the self-assembling of these glycoconjugates.



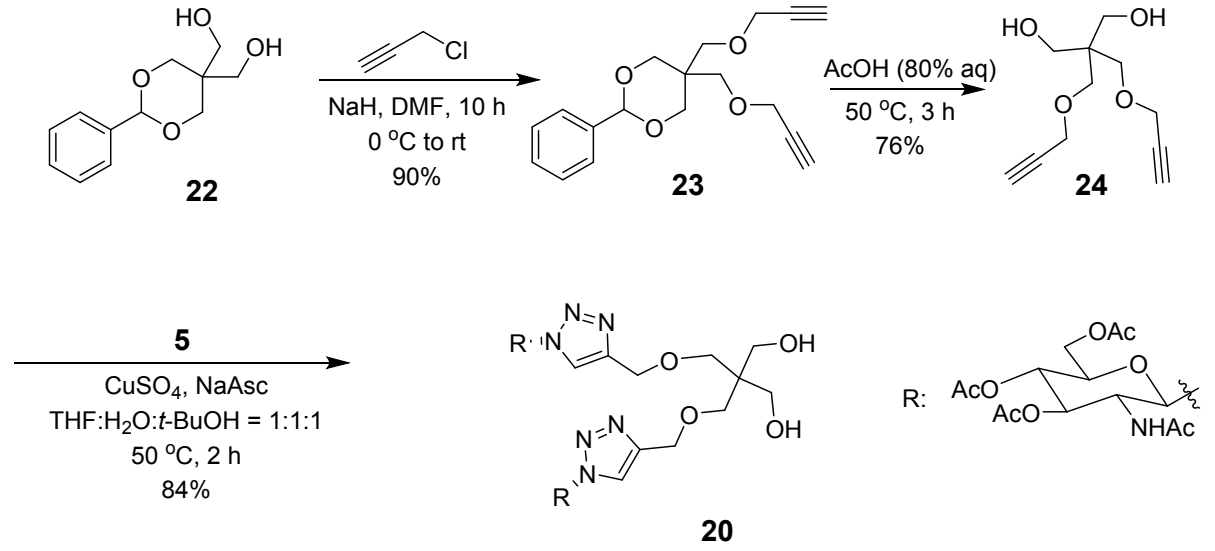
Scheme 1. Synthesis of glycoclusters with different number of triazoles functions **10-15.**

With the successful proof of the design principle provided by the tetra-ester GlcNAc derivatives, we aimed at creating effective gelators using the small molecule propargyl alcohol derivative **2** as the template for a second series of glycoclusters. To help validating the design principle, we again synthesized glycoconjugates with different numbers of sugar triazoles covalently linked. Using the tetra-propargyl ether **9** as the starting material and the GlcNAc azide **5**, four other glycoconjugates were synthesized systematically. As shown in Scheme 2, the four triazole derivatives **16-19** with different degrees of conjugation were synthesized and isolated in a one-pot

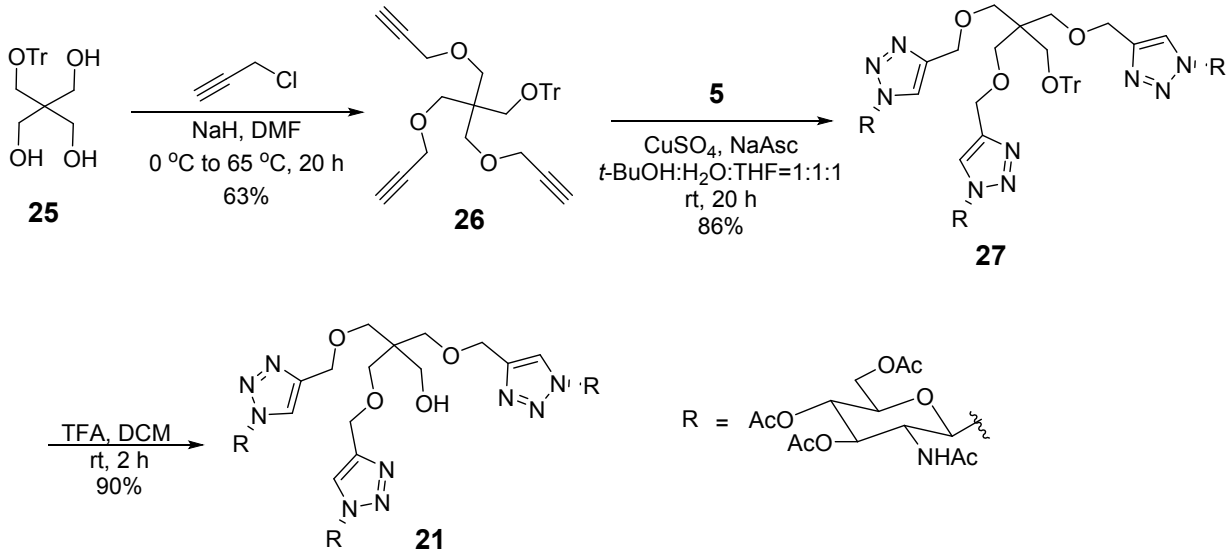
reaction. Here the distance of the triazoles to the tetrahedral carbon center is shorter, triazoles are organized more closely in space and the molecules are more rigid than the tetra-ester linked series. To probe the effect of free hydroxyl functional group, we also synthesized a bis-traizole derivative **20** and a tris-triazole derivative **21**. The synthesis of the compound **20** followed a modified literature procedure (Scheme 3).[38] The tris-triazole glycoconjugate **21** was synthesized using the mono-trityl pentaerythritol[39] as the starting material in a few steps (Scheme 4). The gelation test results of these compounds are also listed in Table 1.



Scheme 2. Synthesis of ether linked pentaerythritol derivatives **16-19** and structures of other triazole glycoconjugates **20** and **21**.



Scheme 3. Synthesis of bis-triazole derivative **20**.



Scheme 4. Synthesis of tris-triazole derivative **21**.

Compounds **16-19** showed similar trend with the tetra-ester series. The mono-triazole derivative **16** did not form any gels and the bis-triazole derivative **17** did not form gels in any of the tested

solvents except water. The tri-functionalized triazole derivative **18** formed gels in most of the alcohols and ethanol water mixture at relatively high concentrations. The best performing gelator molecule was the tetra-functionalized compound **19**. It formed gels in nine of the tested solvents at concentrations ranging from 4.0 to 20.0 mg/mL. Similar to tetra-ester derivative **13**, the tetra-ether derivative **19** formed gels in all tested alcohols. In addition, the tetra-ether **19** also formed gels in ethanol water mixtures and DMSO water mixtures. Again, we observed a clear tendency that increasing number of sugars led to enhanced gelation.

The tetra-ether derivatives exhibited more versatile gelation properties compared to the corresponding tetra-ester derivatives. All the ether derivatives except compound **16** were found to be effective gelators for at least one solvent. The bis-triazole derivative **17** forming a hydrogel supports the trend that covalently linking the sugar moieties has a positive effective on gelation. The analogous conjugates without the propargyl substituents, the bis-triazole **20** and tris-triazole conjugate **21** showed interesting properties in the tested solvents. As what we expected, the tri-functionalized compound **21** with one free hydroxyl group was a very effective gelator. It formed gels in eight of the tested solvents including ethanol, isopropanol, and DMSO:H_2O (v/v, 1:2) mixture, and water. Comparison of the results for the bis-triazole derivative **20** and the tris-triazole derivative **21**, the effect of linking multiple units is clearly shown here too. The tris-triazole derivative **18** with one propargyl group was also an effective gelator for four of the tested solvents; but it was not as effective as the compound **21** with one hydroxyl group. Among all pentaerythritol derivatives, the tetra-functionalized derivative **19** was the most versatile gelator. It formed gels in nine of the tested solvents including five different alcohols and aqueous mixtures. From the twelve various functionalized pentaerythritol derivatives **10-21** discussed above, it is consistent that

trimeric and tetrameric sugar triazole derivatives are more effective gelators than the mono- and bis-triazole derivatives. Some of gel photos are shown in Figure 3.

Table 1. Gelation properties of the glycoconjugates synthesized

No	Tol	EtOH	i-PrOH	n-PrOH	n-BuOH	Glycerol	EtOH: H_2O (1:2)	EtOH: H_2O (1:1)	DMSO: H_2O (1:2)	DMSO: H_2O (1:1)	H_2O
10 (M)	I	S	S	S	S	S	P	P	P	P	P
11 (D)	I	S	S	S	S	S	P	S	P	P	P
12 (Tr)	I	G_T 20.0	G_T 20.0	P	P	S	P	S	P	P	P
13 (Te)	I	G_T 20.0	G_T 4.0	G_T 10.0	G_T 20.0	G_C 20.0	P	S	P	P	P
14 (Te)	P	P	P	P	P	G_C 20.0	P	P	P	P	P
15 (Te)	P	P	S	P	P	G_C 20.0	P	P	P	P	P
16 (M)	S	S	S	S	S	S	P	P	P	P	S
17 (D)	S	S	S	S	S	S	P	P	P	P	G_C 10.0
18 (Tr)	I	P	G_T 10.0	G_T 20.0	G_T 20.0	S	G_T 20.0	P	P	P	I
19 (Te)	I	G_T 6.7	G_T 5.0	G_T 10.0	G_T 10.0	G_C 20.0	G_O 4.0	G_T 20.0	G_T 10.0	G_T 10.0	I
20 (D)	S	S	S	S	S	S	S	S	S	S	S
21 (Tr)	I	G_C 20.0	G_T 10.0	G_C 5.0	G_C 4.0	G_C 20.0	S	S	G_T 10.0	G_C 20.0	G_O 10.0

G, gel at room temperature, the numbers are the corresponding minimum gelation concentrations (MGCs) in mg/mL; C for clear or transparent; T, translucent; O, opaque; I, insoluble; P, crystallize or precipitate; S, soluble at ~20 mg/mL. All tested samples are insoluble in hexanes and soluble in ethylene glycol and triethylene glycol. Compounds **10-15** are from propargyl ester, **16-21** are from propargyl ether. Mono-(M), di- (D), tri- (Tr), tetra-(Te) functionalized pentaerythritol derivatives

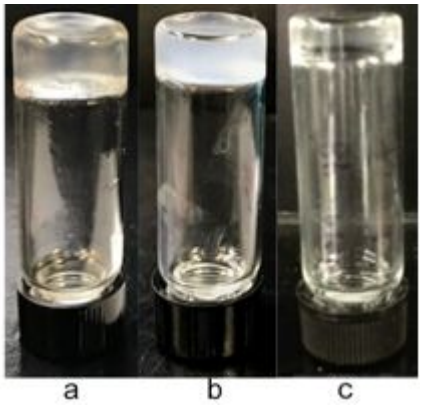


Figure 3. a) A translucent gel formed by compound **13** in i-PrOH at 4.0 mg/mL; b) An opaque gel formed by compound **19** in EtOH:H_2O (v/v, 1:2) at 4.0 mg/mL; c) A clear gel formed by compound **21** in n-butanol at 5.0 mg/mL.

We analyzed the stability of a few selected gels using rheology, the results are shown in Figure 4. The storage moduli G' for all gels were greater than their loss moduli G'' at angular frequency from 0.1-100 rad/s. The hydrogel of compound **21** exhibited greater than 10 kPa G' values at all frequencies. The rheological data indicated that the gels all have viscoelastic properties. The ratio of G'/G'' for these gels are included in the electronic supplementary information (ESI) Tables S2-S4. The amplitude sweep experimental results for the gels are also included in ESI Figures S1-S3.

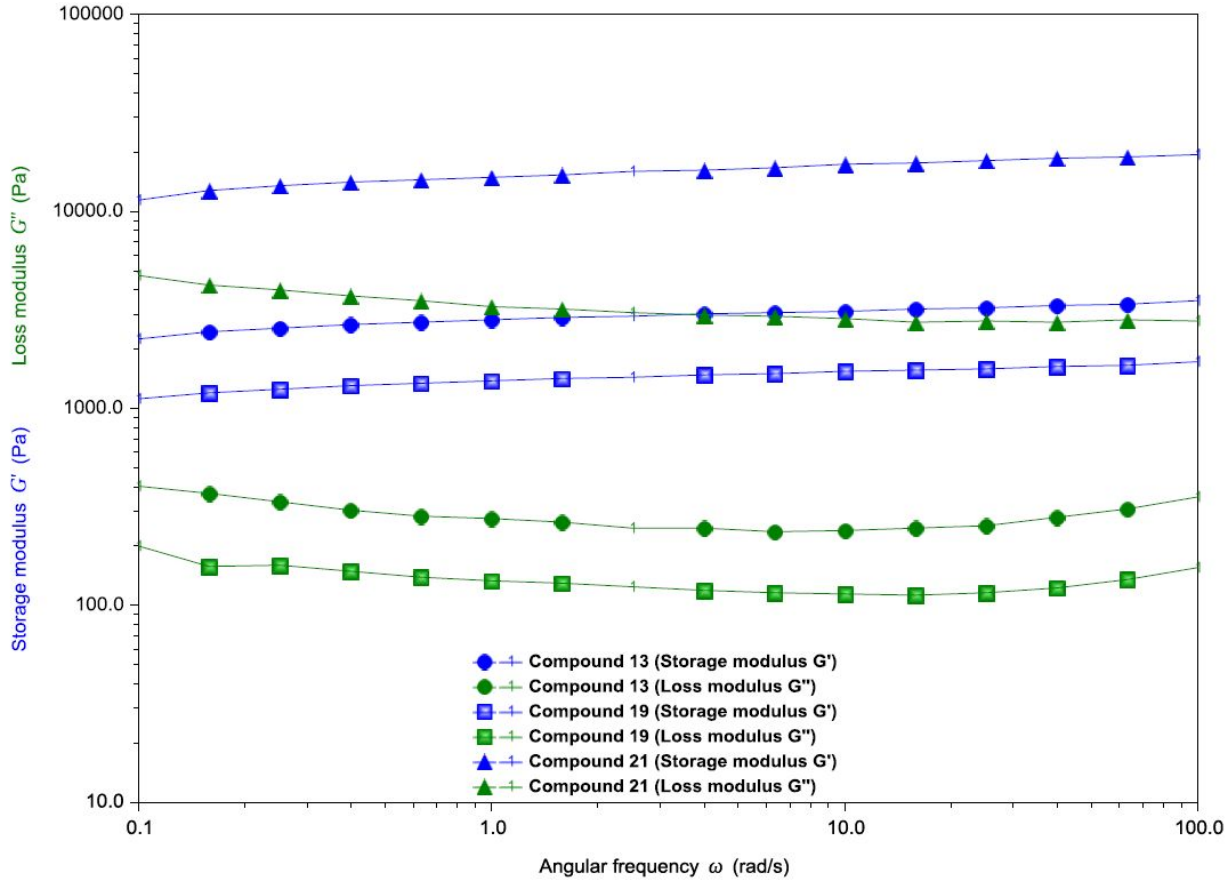


Figure 4. Rheological properties of the gels formed by compound **13** (i-PrOH, 4.0 mg/mL), **19** (EtOH/H_2O, v/v 1:2, 4.0 mg/mL), **21** (H_2O, 10.0 mg/mL), the applied strain was 1% for all samples.

The gel stability was further evaluated by measuring their phase transition temperatures, these are dependent on the solvents in which the gels were formed. As shown in Table 2, the gels in n-butanol had higher melting temperature comparing to DMSO/H_2O gels. For example, the ending melting points of n-butanol gels are close to the boiling point of water. The tetra-ester derivative **13** and tetra-ether derivative **19** had the highest melting points and the tri-ester **18** and tris-ether conjugate **21** had relatively lower melting points. Among the tri-functionalized sugar triazoles, n-butanol gel of **21** had a higher initial melting point. The DMSO-water gel of tetra-ether **19** had a

slightly higher melting point than that of tris-ether **21**. These results indicate that the additional glycosyl triazoles helped with the stability of the branched gels.

Table 2. The melting point range for several gels.

Compound	Concentration (mg/mL)	Solvent system	T_1 (°C)	T_2 (°C)	T_3 (°C)
13	10.0	n-BuOH	50.3	80.7	102.6
18	20.0	n-BuOH	48.4	60.2	95.2
19	10.0	n-BuOH	52.0	83.5	103.3
21	4.0	n-BuOH	59.3	76.4	92.1
19	10.0	DMSO:H_2O (1:1)	34.1	46.2	56.6
21	10.0	DMSO:H_2O (1:1)	32.3	44.2	52.3

The minimum gelation concentration was used to prepare the gels for gel-sol phase transition studies. T_1: initial melting temperature when liquid was first seen. T_2: temperature when the gel is half melted. T_3: the temperature of the entire gel turned into a colorless liquid and the ball reached the bottom of the tube.

To elucidate the gelation and self-assembling properties we analyzed the structures of the tetra-ester **13**, tetra-ether **19**, and trimeric ether **21** using MM2 energy minimization. The chem3D models and structures of compounds **13** and **21** are shown in Figure 5. Compound **13** has a large total polar surface area (tPSA) of 685.96 $Å^2$, and it also has a low LogS value of -10.19, logP=-1.59. The tetra ether **19** has smaller tPSA (617.68$Å^2$) but with improved solubility, with a higher

LogS value of -7.37. This implies that it has a better gelation profile when comparing to the tetra-ester derivative **13**. Compound **21** has a smaller tPSA of 483.49 $Å^2$ and the largest LogS values among these three, -5.05, it also formed a hydrogel. This compound should be suitable for interacting with many drug compounds, which typically have LogS values above -5.0.

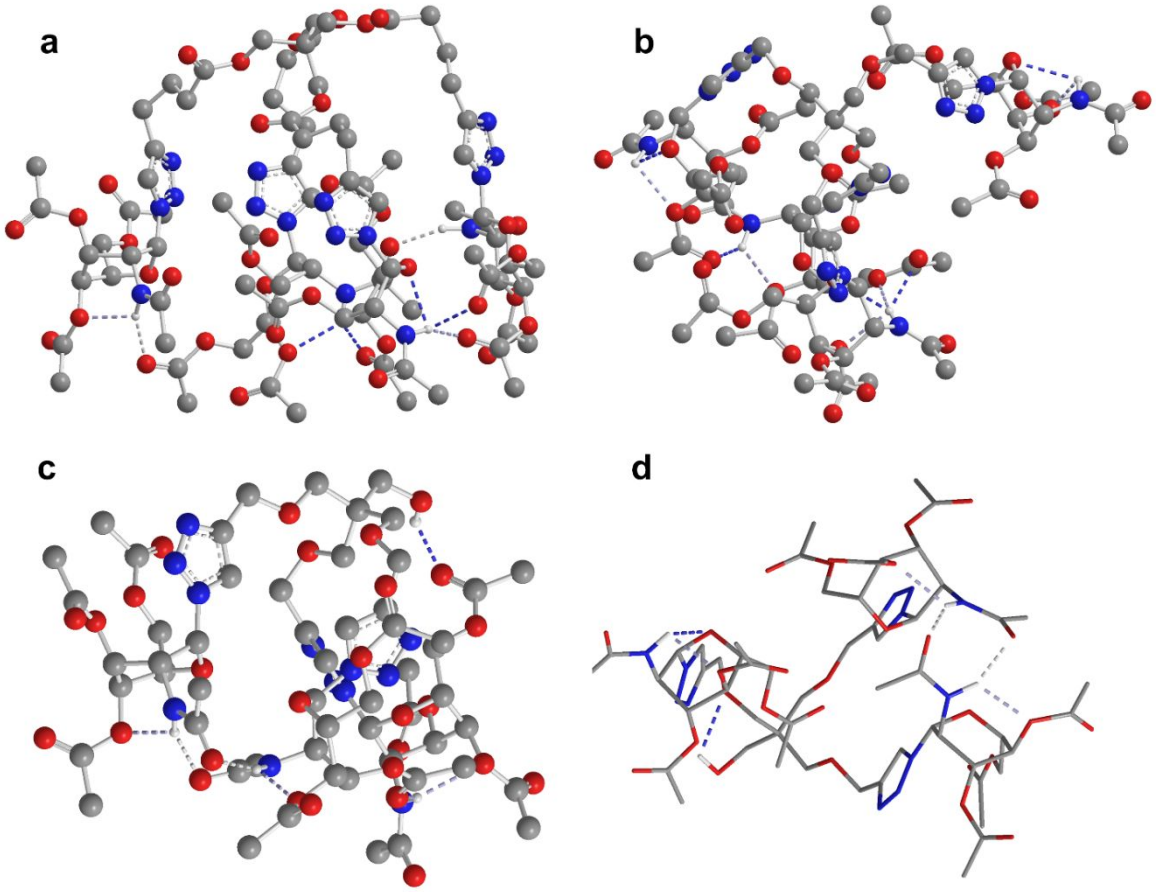


Figure 5. The energy minimized structures from Chem3D for tetra-ester **13** (**a**), tetra-ether **17** (**b**) and compound **21 (c, d)**. For clarity purpose, only polar hydrogen atoms are shown, hydrogen bonds are shown in dashed lines. Compound **21** exhibited inter chain hydrogen bonding and the hydroxyl group also forms hydrogen bonds with a nearby acetyl group. Note the NH is hydrogen bonded with 4-O(Ac) and the oxygen from NHAc of another chain. Another pattern of hydrogen bonding is the NH forming two hydrogen bonds with the ring oxygen and 4-O(Ac) of the same chain.

The self-assembling properties of gelators **13**, **19** and **21** in organic solvents were further studied using ^{1}H NMR spectroscopy studies at different temperatures. As shown in Figures 6, upon increasing temperature from 30 °C to 60 °C, the triazole aromatic C-H chemical shift of gelator **19** moved upfield for δ 0.05 ppm; and the amide signal changed upfield for δ 0.12 ppm. These are similar to the mono-triazole derivatives we reported before.[40] Besides these two main signal changes, the H-2 proton showed a smaller upfield shift from 30 to 60 °C. Similar chemical shift trend of gelators **13** and **21** at variable temperatures was also observed and the results are included in the SI Figures S4 and S5. The triazole ring may participate as a weak hydrogen bond donor and acceptor and may also be involved in π-π interactions or CH-π interactions. At higher temperatures, the intermolecular forces weaken and this resulted in the observed chemical shift changes. The amide signal showed more significant changes of chemical shifts at higher temperature, which is due to the stronger hydrogen bonding interactions of the amide functional groups at lower temperature. Both the amide and the triazole functional groups are important during the supramolecular self-assembly of the glycoclusters. Since the pentaerythritol derivatives are aligned around a tetrahedral center, the intramolecular interactions are limited within the sugar and triazole in the same chain. However, since intermolecular interactions are the most important forces responsible for gelation, we speculate that the compounds will assemble through hydrophobic interactions mainly in aqueous solutions. The branching will not affect the molecular assembly, although packing will occur in a different manner in comparison to the monomer glycoconjugates. The amide signal follows similar trend, that at higher temperature, the intermolecular hydrogen bonding is much weaker. At lower temperature the intermolecular forces are much stronger, which accounted for the gelation formation and stability at r.t. or lower temperatures. The NMR spectra at different temperatures indicated that the amide hydrogen

bonding and triazole π-π interactions were important intermolecular forces in molecular self-assembly. A delicate balance of hydrophilicity and hydrophobicity, intermolecular forces are necessary for effective gelation.

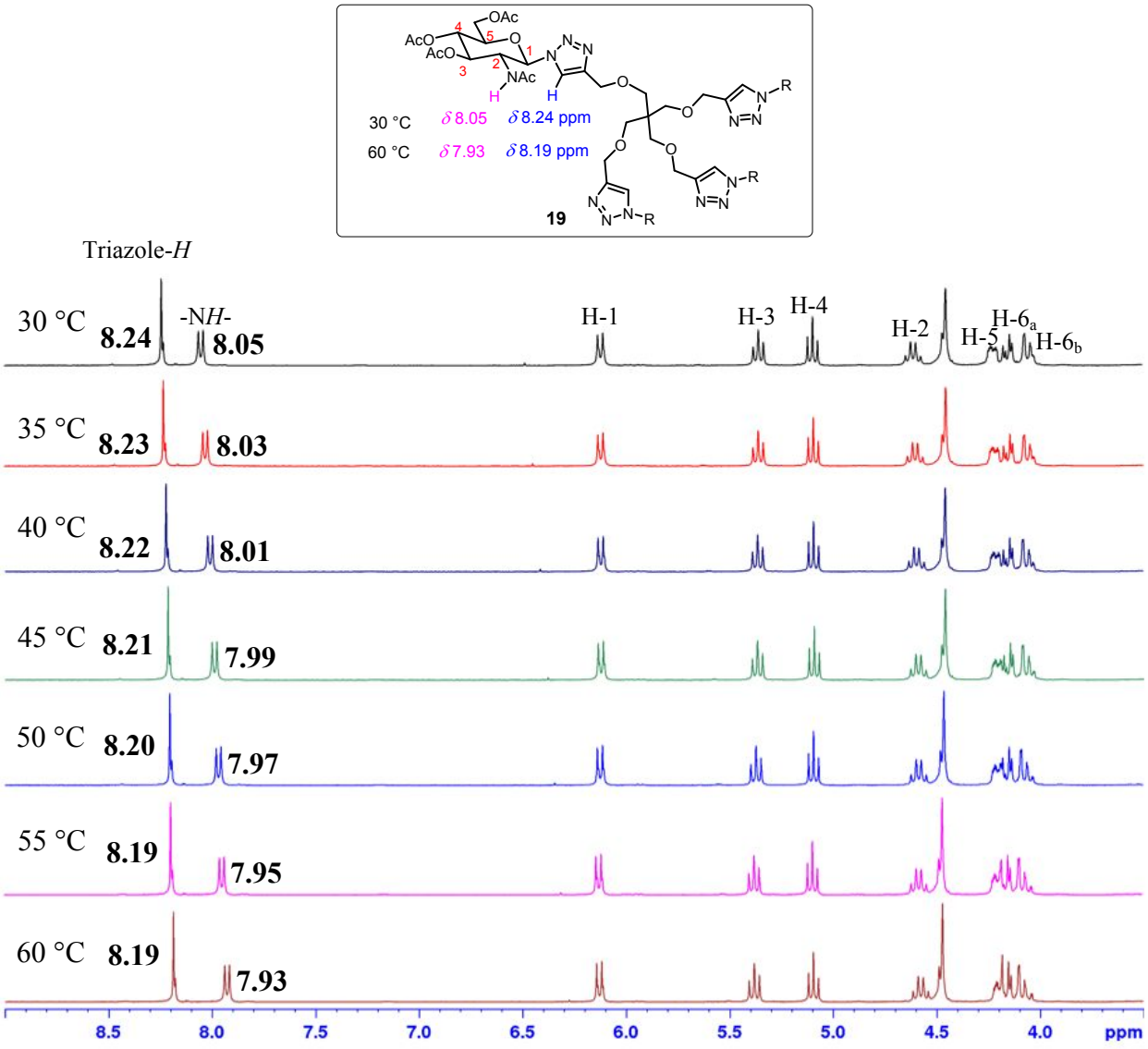


Figure 6. The ^{1}H NMR spectra (3.5 to 9.0 ppm) of compound **19** from 30 °C to 60 °C in d_6-DMSO (10.0 mg/mL).

The tris-triazole derivative **21** formed an opaque hydrogel at 1.0 wt%. We used this hydrogel to encapsulate several drug molecules, including naproxen sodium, vitamin B_2, and vitamin B_{12}. The compound formed stable gels with these drug molecules and the photos of a few selected co-gels are shown in Figure 7. The hydrogel formed by the gelator with naproxen was opaque, similar to the hydrogel formed by pure gelator (Fig. 7a). The vitamin B_2 gels were opaque at higher concentrations (Fig. 7b). With increased amount of riboflavin and further dilution of the gelator with water, the gel turned translucent. The gel showed the typical fluorescence of vitamin B_2 in the dark with UV light irradiation (Fig. 7c). The vitamin B_{12} co-gel was red and translucent (Fig. 7d).

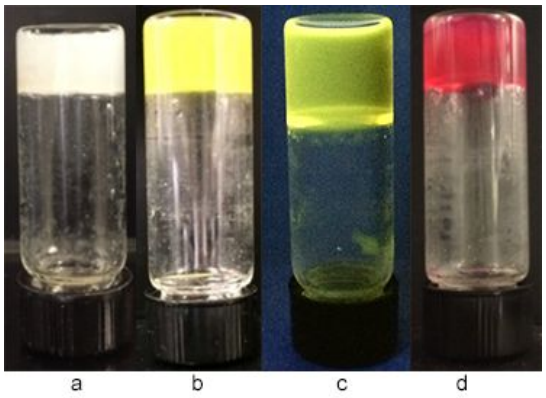


Figure 7. Hydrogels formed by compound **21** with drug molecules. a) Compound **21** (10 mg/mL) and naproxen sodium (0.5 mg/mL); b) Compound **21** (10 mg/mL) and vitamin B_2 (0.1 mg/mL); c) Compound **21** (2.8 mg/mL) and vitamin B_2 (0.83 mg/mL), the gel was viewed under UV light (254 nm) in the dark; d) Compound **21** (10 mg/mL) and vitamin B_{12} (0.3 mg/mL).

We tested riboflavin at different loading and found that the gelator became more effective in presence of riboflavin. The MGC turned from 10 mg/mL for pure compound **21**, to 2.8 mg/mL in presence of riboflavin. The compound formed stable hydrogels with increased amount of vitamin

B_2 loading. Using 10 mg gelator in 1 mL water, riboflavin was added to the gel. We found that the gel was able to trap up to 6 mg of riboflavin. This gel was stable upon further dilution to 3 mL total volume. This is an interesting result because vitamin B_2 is only sparingly soluble in water, we can use the gelator to improve the delivery of vitamin B_2 and increase its solubility in water. We expect that the compound and the co-gels to be useful for the study of molecular self-assembly and formation of two-component gels.

As observed under optical microscope, the hydrogel's morphology changed somewhat upon addition of vitamin B_2 and B_{12}. Without addition of the vitamins, the hydrogel of compound **21** formed very small fibrous network (Fig. 8a). The sample with 0.1 mg/mL concentration of the vitamin B_2 and 10 mg/mL of the gelator **21** showed short clusters of tubules bundled together and some aggregates of the vitamin B_2 shown as yellow spheres (Fig. 8b). When vitamin B_2 concentration increases, the morphology changed drastically to longer fibrous network and the dried gels are more homogeneous. Figure 8c shows the morphology of the gel composed of 2.8 mg/mL gelator and 0.83 mg/mL of vitamin B_2, and the more concentrated gel is shown in Figure 8d, similarly to that of 8c, the gel formed long fibrous network and smooth film-like surface.

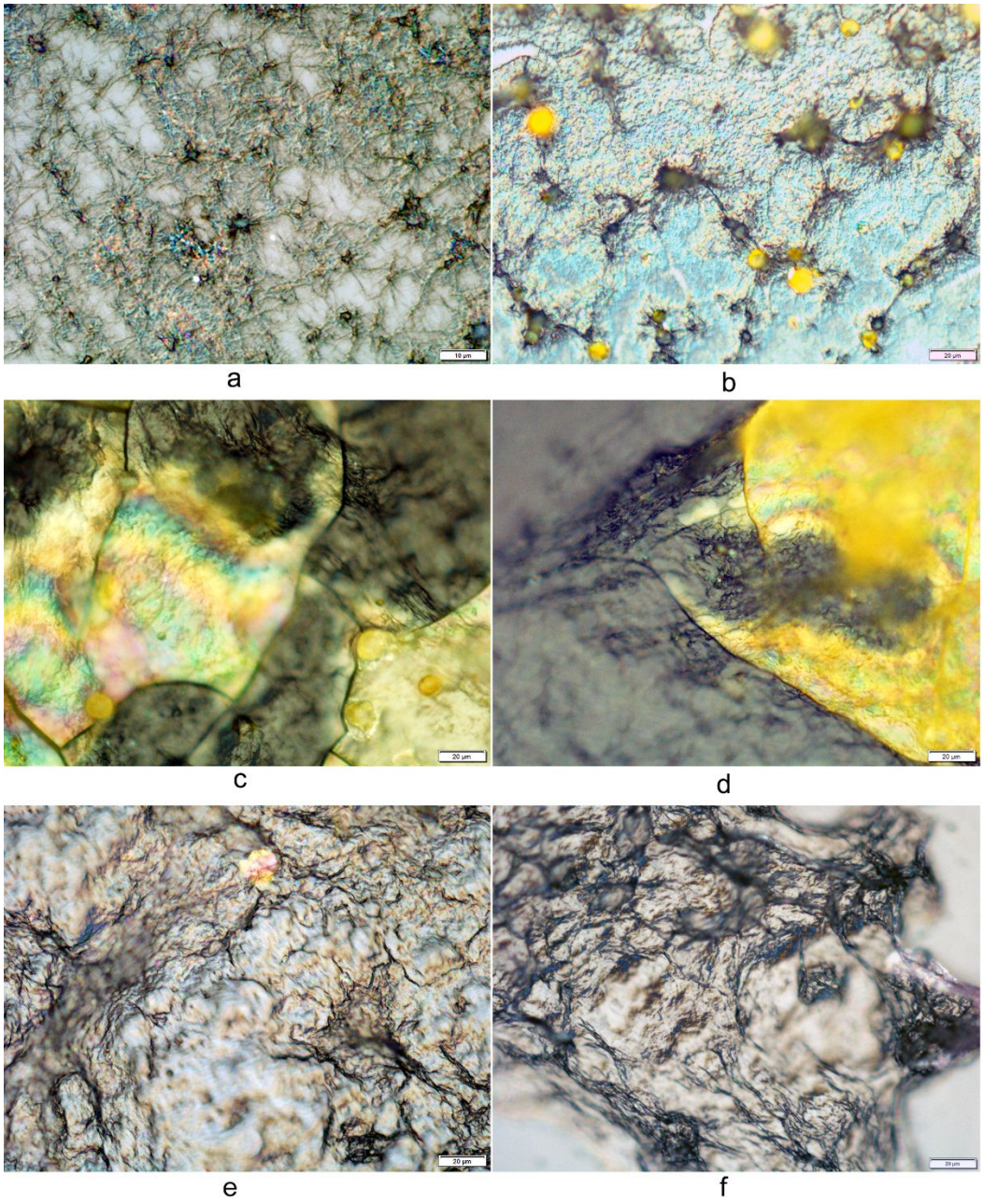


Figure 8. The optical micrographs of the dried hydrogels formed by compound **21** and its co-gels. a) Compound **21** at 10 mg/mL; b) compound **21** at 10 mg/mL and vitamin B_2 at 0.1 mg/mL; c) compound **21** at 2.8 mg/mL and vitamin B_2 at 0.83 mg/mL; d) compound **21** at 3.3 mg/mL and vitamin B_2 at 1.0 mg/mL; e) The morphology of gel phase after the vitamin B_2 release experiment in Figure 11; f) The gel after the vitamin B_{12} release experiment in Figure 12.

We also characterized the morphology of the hydrogel formed by compound **21** using atomic force microscopy (AFM) and observed fibrous assembly motifs. As shown in Figure 9 and Figures S10-S11, the air-dried hydrogel of compound **21** exhibited very thin fibrous networks, height and phase contour AFM images indicated that the fibers formed by the gelator are over 10 μm in length and 0.25 μm in widths (Fig. 9 a, b). The co-gel of compound **21** with vitamin B_2 also showed uniform fibrous network (Fig. 9c) with similar length and width scales.

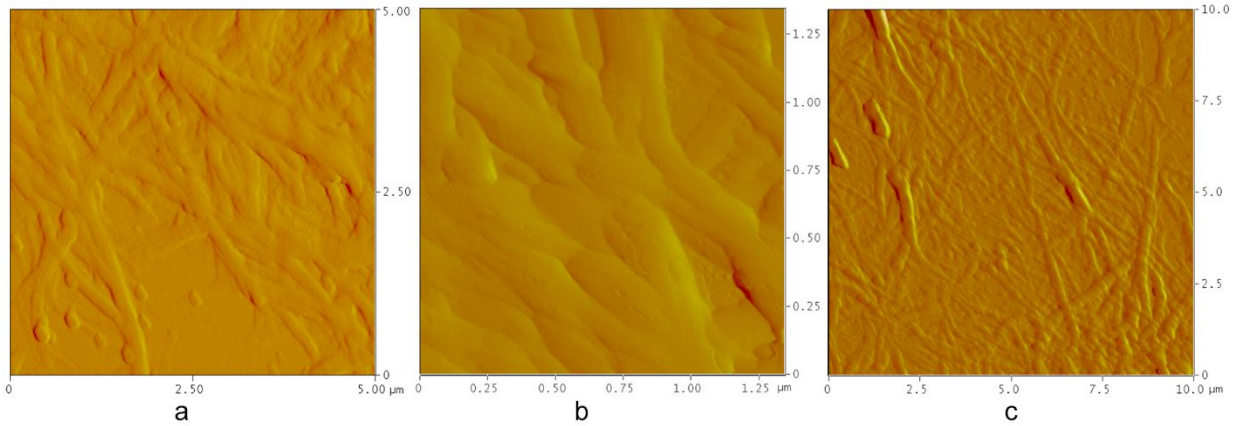


Figure 9. AFM images of the gels formed by compounds **21** in water (a and b) at 10 mg/mL and compound **21** at 10 mg/mL with 0.1 mg/mL of vitamin B_2 (c).

The stability of the gels formed by compounds **21** and **19** was analyzed under alkaline conditions. They were also fully deacetylated using sodium methoxide and methanol, their preparations and characterization are shown in the Supporting Information. The fully deprotected glycoclusters compounds **29** and **30** were not gelators (SI page S10-S12, table S1). They were both soluble in water and aqueous solutions and insoluble in organic solvents; compound **29** was soluble in alcohols but the tetra-ether derivative **30** was not.

The gels formed by the tetra-functionalized compound **19** was stable at pH =12 for over 24 h, these include the gel formed by compound **19** in EtOH/H_2O (v/v 1:2) at 10 mg/mL and the gel of **19** in DMSO/H_2O (v/v 1:1) at 10 mg/mL. The hydrogel formed by compound **21** was stable at pHs of 7 and 10 for up to 24 h, no obvious decomposition of the gels was observed. We also carried out the naproxen release experiment at pH = 10 for compound **21**, similar results were obtained as those of pH = 7, with slightly more release of naproxen into aqueous phase. The experiments are shown in SI Figure S6. These gelator compounds can be hydrolyzed under stronger alkaline conditions or using enzymes. For triggered release of the gel contents, we are continuing with the study of enzymatic deacetylation using lipases or other enzymes. Upon full or partial deacetylation, the gels will be converted to solution.

We also analyzed the drug diffusion from gel phase to aqueous phase. The UV absorbance or fluorescence of the trapped drug molecules was used to monitor the time-dependent release of the drugs from the gels. Figures 10-12 show the drugs released from the gel phase to the aqueous phase at different time points. The gel photos at different times are included in the supplementary information Figures S7-S9. The gel was prepared using 10 mg of compound **21** and 0.5 mg of naproxen sodium in 1 mL water. After a stable gel was obtained, 2 mL water was then added on top of the sample. As shown in Figure 10, naproxen slowly released from the gel phase to aqueous phase. In 16 h approximately 90% of naproxen reached the aqueous phase. For vitamin B_2 release study, in 14 h about 96% vitamin B_2 diffused to the water phase from the gel phase (Figures 11 and S8). Vitamin B_{12} fully diffused from gel phase to aqueous phase in 32 h as shown in Figure 12. The gels were stable after the release period (Figure S9). The morphology of the dried gels was similar to that of the hydrogel of **21** with riboflavin (Fig. 8c). Fig. 8e shows the morphology of the

gel phase after drug release study, the estimated concentration of vitamin B_2 was 0.033 mg/mL and 10 mg/mL gelator **21**, the morphology changed to longer fibrous network and smooth films (Fig. 8e). The gel after vitamin B_{12} release showed similar morphology to those of vitamin B_2 gel, forming fibrous network and film like feature (Fig. 8f).

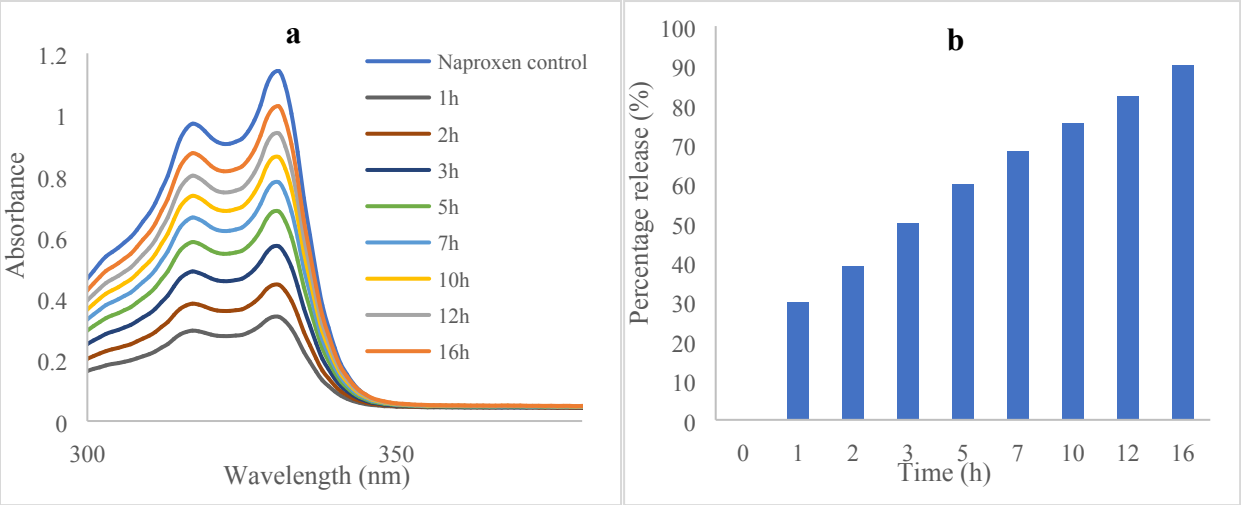


Figure 10. Release of naproxen from gel to aqueous phase. a) UV spectra of naproxen from aqueous phase. The gel was formed by 10 mg of compound **21** in 1.0 mL H_2O (pH 7) with 0.5 mg of naproxen, then 2.0 mL of water was added on top of the gel; naproxen control was prepared by dissolving 0.5 mg naproxen in 3.0 mL of water (pH 7). b) The percent release of naproxen at different time, this was calculated using absorbance at 330 nm at different time versus the standard.

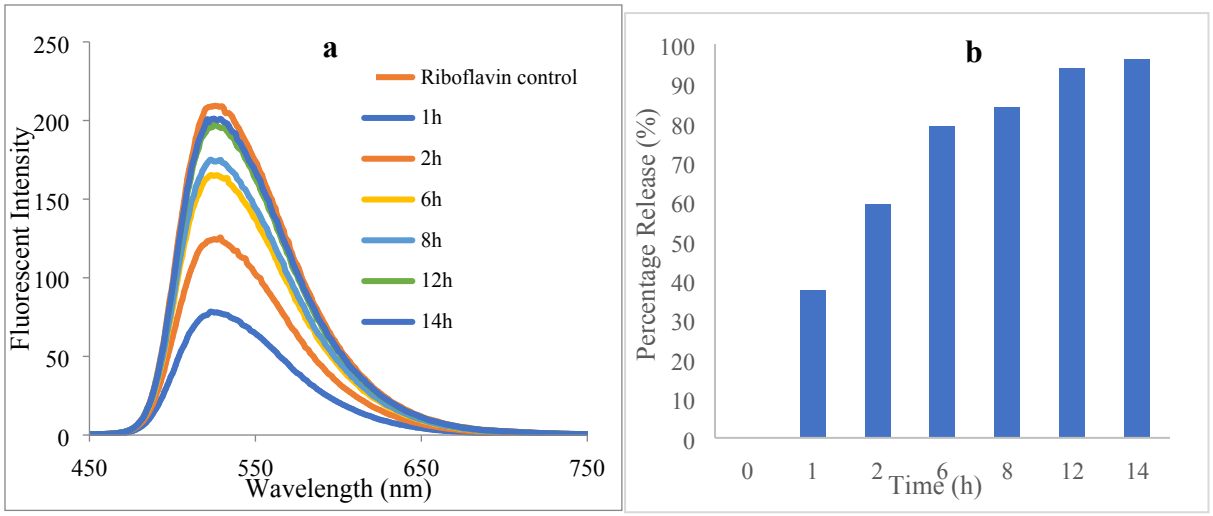


Figure 11. Release of riboflavin from gel to aqueous phase. a) Fluorescence spectra of the riboflavin aqueous phase at different time points. The gel was formed by 10 mg of compound **21** in 1.0 mL H_2O (pH 7) with 0.1 mg of riboflavin, then 2.0 mL of water was added on top of the gel; riboflavin control was prepared by dissolving 0.1 mg riboflavin in 3.0 mL of water (pH 7). b) The percent release of vitamin B_2 at different time, this was calculated using the ratio of fluorescent intensity at different time versus the standard at 526 nm.

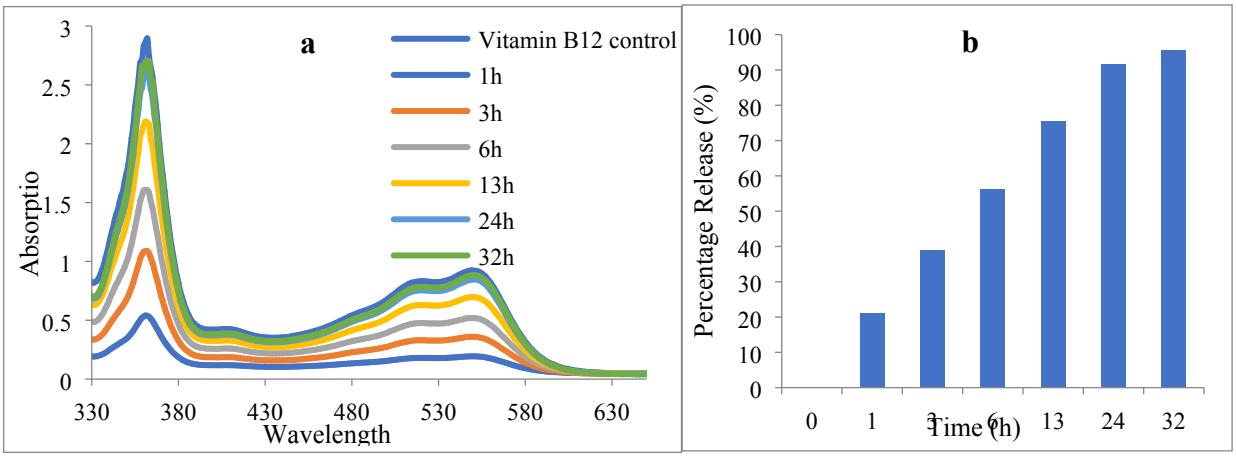


Figure 12. Release of vitamin B_{12} from gel to aqueous phase. a) UV spectra of the vitamin B_{12} from the aqueous phase at different time. The gel was formed by 10 mg of compound **21** in 1.0 mL H_2O with 0.3 mg of vitamin B_{12}, then 2.0 mL of water was added on top of the gel; vitamin B_{12} control was prepared by dissolving 0.3 mg vitamin B_{12} in 3.0 mL of water. b) The percent release of vitamin B_{12} at different times, this was calculated using absorbance at different time versus the standard at 550 nm.

Conclusions

We have designed and synthesized a series of twelve branched compounds functionalized with protected glucose or glucosamine moieties through click chemistry. Pentaerythritol derivatives were used as the core structures to obtain mono-, di-, tri-, and tetra- sugar triazole conjugates. In general, we found that increasing the number of sugar units in the molecules led to enhancement of gelation properties. For the pentaerythritol ester series, the gelation properties of the tetrameric derivatives were affected by the structures of the carbohydrates. The tetra-ester derivative **13** with per-acetylated glucosamine triazoles was an effective gelator, while the per-acetylated glucose and galactose triazoles were not. The pentaerythritol ether derivatives performed better than the corresponding ester derivatives, and the compound **19** was the most efficient gelator in the same

series. The gels were characterized using optical microscopy, rheology, and AFM. The tris-triazole derivative **21** also formed stable hydrogels with naproxen, vitamin B_2 and B_{12}. The co-gels of **21** with a small amount of drug compounds showed time dependent sustained release of the trapped drugs from gel to aqueous phase. These compounds will be further studied for their applications as matrices for cell growth and enzyme immobilization, controlled release delivery of drugs or biomolecules, and as stimuli-responsive smart materials. The results indicate that the design principle of covalently linking suitable small molecules that are not gelators but contain functional groups that can participate in collective non-covalent interactions is a valid strategy in the rational design of supramolecular gelators. We demonstrated that pentaerythritol derivatives containing tris-and tetra- per-acetylated N-acetyl glucosamine triazoles were effective gelators. This structure-based strategy could be applied to other types of glycoconjugates using different branched building blocks. The design rationale can also be applied to other systems to understand the molecular assemblies and to obtain useful soft biomaterials.

Experimental section

General

Reagents and solvents were used as they were received from the suppliers. All purification was conducted by flash chromatography using 230-400 mesh silica gel with a gradient of solvent systems. ^{1}H NMR and proton-decoupled ^{13}C NMR spectra were obtained with Bruker 400 MHz NMR spectrometer in DMSO-d_6, D_2O or $CDCl_3$. The chemical shifts were reported using $CDCl_3$/DMSO-d_6 as internal standard at 7.26/2.50 ppm and at 77.00/39.50 ppm, respectively. 2D NMR experiments (HSQC, COSY) were also conducted using a 400 MHz Bruker NMR spectrometer to assist the proton and carbon signal assignment. Melting point measurements were

carried out using a Fisher Jones melting point apparatus. Rheology experiment was done using a HR-2 Discovery Hybrid Rheometer from TA instrument and a 25 mm Peltier Plate. AFM measurements were carried out using Veeco Dimension 3100 Atomic Force Microscope. The tips used were Tap300-G silicon AFM probes with a resonant frequency of 300 KHz and a force constant of 40 N/m. The molecular mass was measured using LCMS on an Agilent 6120B Single Quad Mass Spectrometer and LC1260 system. HRMS analyses of the glycoclusters were completed with positive electrospray ionization on a Bruker 12 T APEX-Qe FTICR-MS with an Apollo II ion source.

General procedure for the one-pot synthesis of glycoclusters with different number of triazoles

To a 50 mL round bottomed flask, **5** (2 equiv.), tetra-alkyne (1 equiv.), $CuSO_4$ (0.4 equiv.), L-ascorbate sodium salt (0.8 equiv.) were added in the given order. Then to the mixture, 9 mL of *t*-BuOH: H_2O: THF (v/v/v=1:1:1) was added and the reaction mixture was stirred at room temperature for 24 hours under nitrogen atmosphere. Solvent was removed under reduced pressure to give the crude, which was purified by column chromatography using eluent from pure DCM to 5% MeOH/DCM to afford four products, which are mono-, di-, tri- and tetrameric sugar triazoles.

One-pot synthesis of ester linked glycoclusters 10-13

The four compounds were synthesized and isolated from a one-pot reaction of compound **5** (200 mg, 0.538 mmol, 2 equiv.) with compound **8** (137 mg, 0.269 mmol, 1 equiv.) using $CuSO_4$ (13 mg, 0.108 mmol, 0.4 equiv.) and L-ascorbic acid sodium salt (43 mg, 0.216 mmol, 0.8 equiv.) as the catalysts. Four products **10-13** were isolated through flash column chromatography, the isolated yield and characterization data for these four compounds are listed below.

Compound **10** was obtained as an off-white solid, 26 mg, 0.029 mmol; R_f = 0.5 in 5% MeOH/DCM; m.p. 60.0-62.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 5.95 (m, 2H), 5.23 (t, J = 9.7 Hz, 1H), 5.23 (t, J = 9.7 Hz, 1H), 4.61-4.51 (m, 1H), 4.29 (dd, J = 12.5, 4.9 Hz, 1H), 4.19-4.09 (m, 9H), 4.01-3.96 (m, 1H), 2.76 (m, 2H), 2.47 (t, J = 7.4 Hz, 6H), 2.38 (m, 2H), 2.26 (dt, J = 6.8, 2.6 Hz, 6H), 2.08-2.05 (m, 11H), 1.99 (t, J = 2.6 Hz, 3H), 1.88-1.78 (m, 6H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 172.0, 170.0, 169.5, 169.29, 169.25, 146.2, 120.7, 84.7, 83.5, 73.3, 72.3, 71.6, 68.1, 62.1, 61.8, 52.0, 41.7, 32.4, 32.2, 24.1, 23.9, 23.3, 22.2, 20.5, 20.4, 20.2, 17.0; HRMS (ESI+) ($[M + H]^+$) m/z calcd for $C_{43}H_{57}N_4O_{16}$, 885.3764, found 885.3769.

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Compound **11** was obtained as a white solid, 30 mg, 0.024 mmol; R_f = 0.4 in 5% MeOH/DCM; m.p. 90.2-91.7 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.04-7.99 (m, 4H), 6.03 (d, J = 9.9 Hz, 2H), 5.33 (t, J = 9.7 Hz, 2H), 5.08 (t, J = 9.7 Hz, 2H), 4.62-4.50 (m, 2H), 4.26-4.19 (m, 2H), 4.17-4.02 (m, 12H), 2.76 (t, J = 2.6 Hz, 2H), 2.63 (t, J = 7.4 Hz, 4H), 2.40 (t, J = 7.4 Hz, 4H), 2.34 (t, J = 7.4 Hz, 4H), 2.18 (dt, J = 7.0, 2.6 Hz, 4H), 2.01 (s, 6H), 1.99 (s, 6H), 1.94 (s, 6H), 1.86-1.78 (m, 4H), 1.73-1.64 (m, 4H), 1.57 (s, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.2, 172.0, 170.0, 169.5, 169.29, 169.26, 146.2, 120.7, 84.7, 83.5, 73.3, 72.3, 71.6, 68.1, 62.1, 62.0, 61.8, 52.0, 41.7, 32.4, 32.2, 24.1, 23.9, 23.3, 22.2, 20.44, 20.36, 20.2, 17.0.LC-MS (ESI+) m/z calcd for $C_{57}H_{77}N_8O_{24}$ $[M + H]^+$ 1257.5, found 1257.4. HRMS (ESI+) ($[M + 2Na]^{2+}$) m/z calcd for $[C_{57}H_{76}N_8O_{24}Na_2]/2$, 651.2378, found 651.2373.

Compound **12** was obtained as an off-white solid, 63 mg, 0.038 mmol; R_f = 0.22 in 5% MeOH/DCM; m.p. 168.0-170.0 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.05-8.00 (m, 6H), 6.03 (d,

J = 9.9 Hz, 3H), 5.33 (t, *J* = 9.8 Hz, 3H), 5.08 (t, *J* = 9.8 Hz, 3H), 4.56 (m, 3H), 4.25-4.19 (m, 3H), 4.18-4.02 (m, 14H), 2.74 (t, *J* = 2.6 Hz, 1H), 2.63 (t, *J* = 7.4 Hz, 6H), 2.40 (t, *J* = 7.4 Hz, 2H), 2.34 (t, *J* = 7.4 Hz, 6H), 2.18 (dt, *J* = 7.0, 2.6 Hz, 2H), 2.01 (s, 9H), 1.99 (s, 9H), 1.94 (s, 9H), 1.87-1.77 (m, 6H), 1.73-1.63 (m, 2H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.2, 172.0, 170.0, 169.5, 169.28, 169.26, 146.2, 120.7, 84.7, 83.5, 73.3, 72.3, 71.6, 68.1, 62.0, 61.8, 52.0, 41.8, 32.4, 32.2, 24.1, 23.9, 23.3, 22.2, 20.43, 20.35, 20.2, 17.0; LC-MS (ESI+) m/z calcd for $C_{71}H_{97}N_{12}O_{32}$ $[M + H]^+$ 1629.6, found 1629.5,HRMS (ESI+) ($[M + Na]^+$) m/z calcd for $C_{71}H_{96}N_{12}O_{32}Na$, 1651.6146, found 1651.6143.

Compound **13** was isolated as an off-white solid, 130 mg, 0.065 mmol in the one-pot reaction. It was also obtained directly by reacting compound **5** with 4.4 equiv. of azide **8** in 81% yield. R_f = 0.08 in 5% MeOH/DCM; m.p. 219.0-221.0 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.04-7.99 (m, 8H), 6.03 (d, *J* = 9.9 Hz, 4H), 5.33 (t, *J* = 9.6 Hz, 4H), 5.08 (t, *J* = 9.6 Hz, 4H), 4.57 (m, 4H), 4.25-4.18 (m, 4H), 4.18-4.02 (m, 16H), 2.63 (t, *J* = 7.4 Hz, 8H), 2.34 (t, *J* = 7.4 Hz, 8H), 2.01 (s, 12H), 1.99 (s, 12H), 1.94 (s, 12H), 1.82 (m, 8H), 1.57 (s, 12H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.2, 170.0, 169.5, 169.3, 146.2, 120.7, 84.7, 73.3, 72.3, 68.1, 61.9, 61.8, 52.1, 41.8, 32.4, 24.1, 23.9, 22.2, 20.42, 20.35, 20.2. HR-MS (ESI+) ($[M + 2Na]^{2+}$) m/z calcd for $[C_{85}H_{116}N_{16}O_{40}Na_2]/2$: 1023.3660, found 1023.3645.

Synthesis of tetrameric glucosyl triazole derivative 14 Compound **14** was synthesized using compound **8** and 4.4 equivalent of compound **6** (100 mg, 0.268 mmol) under the same click reaction conditions described above. The product was obtained as white solid (98 mg, 0.049 mmol) in 80% yield, R_f = 0.2 in 5% MeOH/DCM, m.p. 113.0-115.0 °C; ^{1}H NMR (400 MHz, d_6-DMSO)

δ 8.16 (s, 4H, -N-C*H*=C-), 6.28 (d, J = 8.7 Hz, 4H, H-1), 5.66-5.50 (m, 8H, H-2, H-3), 5.16 (t, J = 9.6 Hz, 4H, H-4), 4.39-4.32 (m, 4H, H-5), 4.17-4.00 (m, 16H, H_a-6, H_b-6, -O-*C*H_2-C), 2.64 (t, J = 7.3 Hz, 8H, -C*H*$_2$-C=CH-N-), 2.36-2.30 (m, 8H, -C*H*$_2$-C=O), 2.03 (s, 12H, -C*H*$_3$), 1.99 (s, 12H, -C*H*$_3$), 1.96 (s, 12H, -C*H*$_3$), 1.86-1.75 (m, 20H, 4x -CH$_2$-C*H*$_2$-CH$_2$-, 4x -C*H*$_3$); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.3, 169.9, 169.5, 169.3, 168.4, 146.8 (-N-CH=*C*-), 120.9 (-N-*C*H=C-), 83.7 (C-1), 73.2 (C-5), 72.1 (C-3), 70.2 (C-2), 67.6 (C-4), 62.3 (-O-*C*H$_2$-C-), 61.7 (C-6), 42.8 (-O-CH$_2$-*C*-), 32.5, 24.1, 23.9, 20.4, 20.3, 20.2, 19.7; LC-MS (ESI+) ([M + 2H]$^{2+}$) m/z calcd for [$C_{85}H_{114}N_{12}O_{44}$]/2, 1003.4, found 1003.4. HRMS (ESI+) ([M + 2Na]$^{2+}$) m/z calcd for [$C_{85}H_{112}N_{12}O_{44}Na_2$]/2, 1025.3340, found 1025.3326.

Synthesis of tetrameric galactosyl triazole derivative 15 Compound **15** was synthesized using 1 equiv. of compound **8** and 4.4 equiv. of compound **7** (160 mg, 0.431 mmol) using 0.4 equiv. of CuI as catalyst. The desired product was obtained as an off-white solid (147 mg, 0.073 mmol) in 75% yield, R_f = 0.5 in 5% MeOH/DCM. m.p. 125.0-127.0 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.06 (s, 4H, -N-C*H*=C-), 6.19 (d, J = 9.0 Hz, 4H, H-1), 5.53 (t, J = 9.2 Hz, 4H, H-2), 5.47-5.39 (m, 8H, H-3, H-4), 4.60-4.54 (m, 4H, H-5), 4.16-4.06 (m, 12H, -O-*C*H$_2$-C-, H_a-6), 4.01 (dd, J = 11.5, 7.2 Hz, 4H, H_b-6), 2.64 (t, J = 7.4 Hz, 8H, -C*H*$_2$-C=CH-N-), 2.33 (t, J = 7.4 Hz, 8H, -C*H*$_2$-C=O), 2.17 (s, 12H, -C*H*$_3$), 1.98 (s, 12H, -C*H*$_3$), 1.93 (s, 12H, -C*H*$_3$), 1.88-1.81 (m, 8H, -CH$_2$-C*H*$_2$-CH$_2$-), 1.79 (s, 12H, -C*H*$_3$); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.2, 170.0, 169.9, 169.5, 168.5, 146.8 (-N-CH=*C*-), 121.2 (-N-*C*H=C-), 84.2 (C-1), 72.9 (C-5), 70.4 (C-3), 67.9 (C-2), 67.3 (C-4), 61.9 (-O-*C*H$_2$-C-), 61.5 (C-6), 41.8 (-O-CH$_2$-*C*-), 32.5, 24.02, 24.00, 20.4, 20.33, 20.26, 19.9; HRMS (ESI+) ([M + 2H]$^{2+}$) m/z calcd for [$C_{85}H_{114}N_{12}O_{44}$]/2, 1003.3520, found 1003.3497.

One-pot synthesis of ether linked glycoclusters 16-19

The four compounds were synthesized and isolated from a one-pot reaction of compound **5** (200 mg, 0.538 mmol, 2 equiv.) with compound **9** (77 mg, 0.269 mmol, 1 equiv.), using $CuSO_4$ (13 mg, 0.108 mmol, 0.4 equiv.) and L-ascorbate sodium salt (43 mg, 0.216 mmol, 0.8 equiv.) as the catalysts. Four products **16-19** were isolated through column chromatography, the characterization data for these four compounds are listed below.

Compound **16** was obtained as an off-white solid, 19 mg, 0.029 mmol; R_f = 0.35 in 5% MeOH /DCM; m.p. 63.0-65.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H, -N-C*H*=C-), 6.46 (d, *J* = 9.1 Hz, 1H, -N*H*-), 6.10 (d, *J* = 10.0 Hz, 1H, H-1), 5.53 (t, *J* = 9.9 Hz, 1H, H-3), 5.22 (t, *J* = 9.9 Hz, 1H, H-4), 4.67-4.51 (m, 3H, -N-CH=C-CH_2-O-, H-2), 4.30 (dd, *J* = 12.6, 4.9 Hz, 1H, H_a-6), 4.16-4.08 (m, 7H, 3x -CH_2-C≡CH, H_b-6), 4.06-4.00 (m, 1H, H-5), 3.51 (s, 6H, 3x -CH_2-O-CH_2-C≡CH), 3.49 (s, 2H, -N-CH=C-CH_2-O-CH_2-), 2.43 (t, *J* = 2.4 Hz, 3H, 3x -C≡C*H*), 2.06 (s, 3H, -CH_3), 2.05 (s, 6H, -CH_3), 1.76 (s, 3H, -CH_3 in -NHAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.54, 170.5, 169.3, 146.1 (-N-CH=*C*-), 121.8 (-N-*C*H=C-), 85.6 (C-1), 80.1 (-*C*≡CH), 74.9 (C-5), 74.3 (-C≡*C*H), 72.3 (C-3), 69.2 (-N-CH=C-CH_2-O-*C*H_2-), 68.8 (-*C*H_2-O-CH_2-C≡CH), 68.1 (C-4), 64.9 (-N-CH=C-*C*H_2-O-), 61.7 (C-6), 58.6 (-*C*H_2-C≡CH), 53.6 (C-2), 44.9 (-*C*-CH_2-O-CH_2-C≡CH), 22.8 (-*C*H_3 in NHAc), 20.7, 20.59, 20.55. HRMS (ESI+) ([M + H]$^+$) m/z calcd for $C_{31}H_{41}N_4O_{12}$, 661.2715, found 661.2710.

Compound **17** was obtained as a white solid, 28 mg, 0.027 mmol; R_f = 0.25 in 5% MeOH/DCM; m.p. 171.0-173.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 2H, -N-C*H*=C-), 6.79 (d, *J* = 9.2 Hz, 2H, -N*H*-), 6.15 (d, *J* = 9.9 Hz, 2H, H-1), 5.50 (t, *J* = 9.2 Hz, 2H, H-3), 5.36 (t, *J* = 9.2 Hz, 2H,

H-4), 4.76-4.64 (m, 2H, H-2), 4.61-4.49 (m, 4H, 2x -N-CH=C-CH_2-O-), 4.35 (dd, J = 12.5, 4.8 Hz, 2H, H_a-6), 4.21 (dd, J = 12.5, 2.0 Hz, 2H, H_b-6), 4.13-4.06 (m, 6H, 2x -CH_2-C≡CH, 2x H-5), 3.50-3.38 (m, 8H, 2x -CH_2-O-CH_2-C≡CH, 2x -N-CH=C-CH_2-O-CH_2-), 2.41 (t, J = 2.3 Hz, 2H, 2x -C≡CH), 2.07 (s, 6H, -CH_3), 2.06 (s, 6H, -CH_3), 2.04 (s, 6H, -CH_3), 1.74 (s, 6H, -CH_3 in -NHAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.7, 170.6, 169.4, 145.5 (-N-CH=*C*-), 122.1 (-N-*C*H=C-), 85.7 (C-1), 80.1 (-*C*≡CH), 75.1 (C-5), 74.2 (-C≡*C*H), 72.7 (C-3), 68.7 (-N-CH=C-CH_2-O-*C*H_2- and -*C*H_2-O-CH_2-C≡CH), 68.1 (C-4), 64.4 (-N-CH=C-*C*H_2-O-), 61.8 (C-6), 58.7 (-*C*H_2-C≡CH), 53.4 (C-2), 44.9 (-*C*-CH_2-O-CH_2-C≡CH), 22.7 (-*C*H_3 in NHAc), 20.7, 20.64, 20.60. LC-MS (ESI+) calcd for $C_{45}H_{61}N_8O_{20}$ $[M+H]^+$ 1033.4 found 1033.3, HRMS (ESI+) ($[M + 2Na]^{2+}$) m/z calcd for $[C_{45}H_{60}N_8O_{20}Na_2]/2$, 539.1854, found 539.1851.

Compound **18** was obtained as a white solid, 30 mg, 0.021 mmol; R_f = 0.17 in 5% MeOH/DCM; m.p. 244.0-246.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 3H, -N-C*H*=C-), 6.95 (d, J = 9.0 Hz, 3H, -N*H*-), 6.19 (d, J = 9.9 Hz, 3H, H-1), 5.54 (t, J = 10.2 Hz, 3H, H-3), 5.33 (t, J = 10.2 Hz, 3H, H-4), 4.71-4.49 (m, 9H, 3x H-2, 3x -N-CH=C-CH_2-O-), 4.34 (dd, J = 12.7, 4.8 Hz, 3H, H_a-6), 4.21 (dd, J = 12.7, 1.9 Hz, 3H, H_b-6), 4.14-4.07 (m, 5H, -CH_2-C≡CH, 3x H-5), 3.50-3.34 (m, 8H, -CH_2-O-CH_2-C≡CH, 3x -N-CH=C-CH_2-O-CH_2-), 2.46 (t, J = 2.3 Hz, 1H, -C≡C*H*), 2.07 (s, 9H, -CH_3), 2.06 (s, 9H, -CH_3), 2.04 (s, 9H, -CH_3), 1.73 (s, 9H, -CH_3 in -NHAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.7, 170.5, 169.4, 145.4 (-N-CH=*C*-), 122.3 (-N-*C*H=C-), 85.6 (C-1), 80.1 (-*C*≡CH), 75.0 (C-5), 74.5 (-C≡*C*H), 72.5 (C-3), 68.7 (-N-CH=C-CH_2-O-*C*H_2-), 68.6 (-*C*H_2-O-CH_2-C≡CH), 68.2 (C-4), 64.3 (-N-CH=C-*C*H_2-O-), 61.8 (C-6), 58.6 (-*C*H_2-C≡CH), 53.6 (C-2), 45.0 (-*C*-CH_2-O-CH_2-C≡CH), 22.7 (-*C*H_3 in NHAc), 20.68, 20.65, 20.61. HRMS (ESI+) ($[M + Na]^+$) m/z calcd for $C_{59}H_{80}N_{12}O_{28}Na$, 1427.5097, found 1427.5104.

Compound **19** was obtained as a white solid, 156 mg, 0.088 mmol. Compound **19** was also synthesized directly using compound **5** with 4.4 equivalent of azide **9** in 83% yield. R_f = 0.06 in 5% MeOH /DCM; m.p. 250.0-252.0 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.24 (s, 4H, -N-C*H*=C-), 8.05 (d, *J* = 9.1 Hz, 4H, -N*H*-), 6.12 (d, *J* = 10.0 Hz, 4H, H-1), 5.36 (t, *J* = 9.8 Hz, 4H, H-3), 5.09 (t, *J* = 9.8 Hz, 4H, H-4), 4.66-4.54 (m, 4H, H-2), 4.45 (s, 8H, -N-CH=C-C*H*$_2$-O-), 4.15 (dd, *J* = 12.5, 5.1 Hz, 4H, H_a-6), 4.06 (dd, *J* = 12.5, 1.8 Hz, 4H, H_b-6), 3.38 (s, 8H, -O-C*H*$_2$-C-), 2.01 (s, 12H, -C*H*$_3$), 1.97 (s, 12H, -C*H*$_3$), 1.95 (s, 12H, -C*H*$_3$), 1.79 (s, 12H, C*H*$_3$ in -NHAc); ^{13}C NMR (100 MHz, d_6-DMSO) δ 170.0, 169.5, 169.4, 169.3, 144.3 (-N-CH=*C*-), 122.6 (-N-*C*H=C-), 84.6 (C-1), 73.4 (C-5), 72.4 (C-3), 69.0 (-O-*C*H$_2$-C-), 68.0 (C-4), 64.1 (-N-CH=C-*C*H$_2$-O-), 61.7 (C-6), 52.0 (C-2), 45.0 (-O-CH$_2$-*C*-), 22.2 (-*C*H$_3$ in NHAc), 20.40, 20.35, 20.2. HR-MS (ESI+) ([M + 2H]$^{2+}$) m/z calcd for [$C_{73}H_{102}N_{16}O_{36}$]/2, 889.3316 found 889.3298.

Compound 20 was synthesized using 1.0 equiv. of compound **24** and 2.2 equiv. of compound **5** in 84% yield (ESI), R_f = 0.5 in 10% MeOH/DCM, m.p. 167.0-169.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 2H), 7.14 (d, *J* = 9.2 Hz, 2H), 6.13 (d, *J* = 9.9 Hz, 2H), 5.49 (t, *J* = 9.7 Hz, 2H), 5.29 (t, *J* = 9.7 Hz, 2H), 4.68-4.54 (m, 6H), 4.36-4.28 (m, 2H), 4.22-4.15 (m, 2H), 4.14-4.08 (m, 2H), 3.58 (s, 4H), 3.51-3.42 (m, 4H), 2.09-2.02 (m, 18H), 1.72 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.7, 170.6, 169.4, 145.2, 122.0, 85.9, 74.9, 72.5, 70.0, 68.1, 64.2, 63.8, 61.8, 53.6, 45.2, 22.6, 20.7, 20.61, 20.57; HRMS (ESI+) ([M + 2Na]$^{2+}$) m/z calcd for [$C_{39}H_{56}N_8O_{20}Na_2$]/2, 501.1698, found 501.1700.

Compound 21 was prepared from compound **27** in 90% yield (ESI). R_f = 0.42 in 10% MeOH/DCM, m.p. 210.0-213.0 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.24 (s, 3H), 8.06 (d, J = 9.2 Hz, 3H), 6.11 (d, J = 9.9 Hz, 3H), 5.34 (t, J = 9.7 Hz, 3H), 5.10 (t, J = 9.7 Hz, 3H), 4.66-4.56 (m, 3H), 4.47 (s, 6H), 4.29-4.20 (m, 3H), 4.15 (dd, J = 12.5, 4.9 Hz, 3H), 4.06 (dd, J = 12.5, 2.0 Hz, 3H), 3.37 (s, 8H), 2.01 (s, 9H), 1.98 (s, 9H), 1.95 (s, 9H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 170.0, 169.53, 169.45, 169.3, 144.4, 122.5, 84.6, 73.4, 72.4, 69.0, 68.0, 64.1, 61.7, 60.1, 52.0, 45.3, 22.2, 20.43, 20.36, 20.2; LC-MS (ESI+) $[M+Na]^+$ m/z calcd for $C_{56}H_{78}N_{12}O_{28}$ 1389.5, found 1389.5, HRMS (ESI+) ($[M + 2Na]^{2+}$) m/z calcd for $[C_{56}H_{78}N_{12}O_{28}Na_2]/2$, 706.2416, found 706.2420.

Supplementary Information Available: Synthesis, characterization data and gelation test result for compound **1** are provided. Copies of ^{1}H and ^{13}C NMR spectra for compounds **8-30** are included. 2D NMR (HSQC and COSY) spectra of compounds **14**, **15**, **19**, **20** are also provided. Additional rheological studies are included. ^{1}H NMR spectra at variable temperatures for compounds **13** and **21** are provided. Naproxen co-gels and release profile with gelator **21** at pH 7 and 10 is summarized. The gel photos of hydrogels formed by compound **21** with naproxen, riboflavin, and vitamin B_{12} at different times are also included. Additional AFM images are also provided.

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