Accepted Manuscript

Synthesis and self-assembling properties of 4,6−benzylidiene acetal protected D-glucose and D-glucosamine β−1,2,3−triazole derivatives

Anji Chen, Ifeanyi Okafor, Consuelo Garcia, Guijun Wang

PII: S0008-6215(17)30694-8

DOI: 10.1016/j.carres.2018.02.011

Reference: CAR 7527

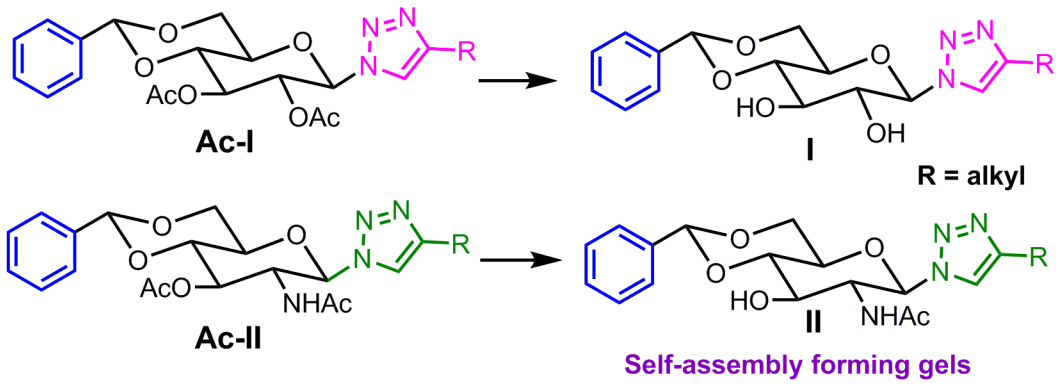
To appear in: *Carbohydrate Research*

Received Date: 22 September 2017

Revised Date: 17 February 2018

Accepted Date: 17 February 2018

Please cite this article as: A. Chen, I. Okafor, C. Garcia, G. Wang, Synthesis and self-assembling properties of 4,6−benzylidiene acetal protected D-glucose and D-glucosamine β−1,2,3−triazole derivatives, *Carbohydrate Research* (2018), doi: 10.1016/j.carres.2018.02.011.



Synthesis and self-assembling properties of 4,6-benzylidiene acetal protected D-glucose and D-glucosamine β-1,2,3-triazole derivatives

Anji Chen, Ifeanyi Okafor, Consuelo Garcia, Guijun Wang*

Department of Chemistry and Biochemistry, Old Dominion University, Norfolk, VA 23529, USA.

*Corresponding Author:

Guijun Wang, PhD

Professor of Chemistry and Biochemistry

Old Dominion University

4541 Hampton Boulevard

Norfolk, VA 23529-0126

Email: g1wang@odu.edu

Telephone: (757) 683-3781

Fax: (757) 683-4628

Abstract:

Sugar based low molecular weight gelators (LMWGs) are useful small molecules that can form reversible supramolecular gels with many applications. Selective functionalization of common monosaccharides has resulted in several classes of effective LMWGs. Recently we found that certain peracetylated sugars containing anomeric triazole functional groups were effective gelators. In this study we synthesized two series of 4,6-*O*-benzylidene acetal protected β-1,2,3-triazolyl glycoside of D-glucose and *N*-acetyl D-glucosamine derivatives and evaluated their self-assembling properties in a few solvents. Several gelators were obtained and the gelation properties of these compounds rely on the structures of the 4-triazolyl substituents. Typically, alkyl derivatives resulted in effective gelation in organic solvents and aqueous mixtures of ethanol and dimethyl sulfoxide. But further acetylation of these compounds resulted in loss of gelation properties. The gels were characterized using optical microscopy, rheology, and FTIR spectroscopy. We also analyzed the molecular assemblies using ^{1}H NMR spectroscopy to probe the influences of the hydroxyl, amide, and triazole functional groups. Naproxen was used as a model drug and it formed co-gels with compound **25** in DMSO water mixtures. Using UV spectroscopy, we found that naproxen was slowly released from the gel to aqueous solution. The general structure and gelation trend obtained here can be useful in designing sugar based biomaterials. We expect that further structural optimization can lead to more effective gelators that are compatible with different drug molecules for encapsulation and sustained release.

Keywords: D-Glucose; D-Glucosamine; Organogelator; Hydrogelator; Triazole; Self-assembling; Benzylidene acetal

Introduction

Carbohydrate based low molecular weight gelators (LMWGs) have received increasing attention over recent years due to their interesting physical chemical properties and many applications.[1-5] The gelators typically self-assemble and form fibrous supramolecular architectures that can immobilize certain solvents and form reversible gels. The driving forces for the formation of supramolecular gel networks are non-covalent forces such as hydrogen bonding, hydrophobic interactions, π-π stacking, CH-π interactions, and van der Walls forces, etc. Low molecular weight organogelators (LMOGs) have shown numerous applications for the formation of new supramolecular materials.[6-8] They have been found to be useful for oil spill recovery by several research groups.[9-22] Organogels were also have studied for drug delivery and biomedical applications.[23,24] For optical electronic device applications the solvents used are typically hydrocarbons and volatile aromatic solvents such as toluene and xylenes. Polar organic solvents such as ethanol, glycerol, ethylene glycol, dimethyl sulfoxide, etc. have been studied for transdermal drug delivery applications using lectin and other gelators. However it is obvious for toxicity and biocompatibility reasons, hydrogels would be more applicable for drug delivery and other biomedical related applications. Supramolecular gels have also been utilized in synthesis and catalysis and environmental applications.[7,25-29] Some proline containing gelators were shown to function as organocatalysts with enhanced catalytic activities in the gel state.[30-33]

The structures of LMWGs encompass a broad range of functionalities and natural products including amino acids, peptides, sugars, lipids etc.[2,3,34-36] Carbohydrates are naturally abundant, renewable resources and they contain multiple chiral centers. Selective functionalization of sugars can afford new soft materials which are likely to be biocompatible and biodegradable. For

instance, several readily available monosaccharides such as D-glucose and D-glucosamine have been modified to form supramolecular gels with many different applications.[37-43] Despite the many advancements on low molecular weight gelators, the rational design of small molecules to function as effective gelators is still challenging. From a chemical structure point of view, we are interested in understanding how the modification of simple sugars can lead to effective molecular gelators and stimuli responsive materials. Previously, Shinkai et al have studied gelation behaviors of 4,6-*O*-benzylidene acetal protected glucose, galactose, mannose, etc. extensively and obtained useful structure and gelation properties relationship, the orientation of the free 2,3-diol plays an important role.[44-48] We have also systematically studied the functionalization of monosaccharides including D-glucose and D-glucosamine to obtain effective LMWGs.[49-53] Further functionalization of hydroxyl groups at certain 4,6-O-benzylidene acetal protected D-glucose afforded functional LMWGs.[54-57]

As shown in Figure 1, certain derivatives of 4,6-*O*-benzylidene acetal protected D-glucose and D-glucosamine derivatives **1** and **2** were found to be effective low molecular weight gelators (LMWGs). Recently we studied the peracetylated D-glucosyl triazoles and D-glucosamine triazole derivatives (**3** and **4**) too and screened their gelation properties in several organic solvents and aqueous mixtures.[51,52] Similarly to the benzylidene acetal derivatives, the peracetylated triazoles are effective organogelators and are able to gelate alcohols, DMSO and water mixtures, ethanol and water mixtures. Many D-glucosamine triazole derivatives are effective low molecular weight hydrogelators too.[52,53] The N-acetyl glucosamine derivatives **4** are more effective at forming hydrogels when R group is long chain alkyl or alkyl with polar functional groups. Based on the discussions of the structural features, we envision that

combining the core structures of the two systems may lead to more effective gelators. Incorporating triazole to the anomeric position of the 4,6-*O*-benzylidene acetal protected glucose or glucosamine will give compounds **I** and **II** (Figure 1), the study of these new compounds may allow us to better understand the structural requirement for effective gelation. The introduction of benzylidene acetal functional groups may prevent gelation in certain solvents since the additional intermolecular forces may be too overwhelming and leads to crystallization or precipitation. From a structural point of view, it is useful to find out whether the popular benzylidene acetal protective group is important for molecular self-assembly and gelation when combined with triazole functional groups. As part of our effort in understanding structure and gelation property relationships and rational design of effective supramolecular gelators that can respond to different physical and chemical environment, we designed and synthesized a series of monosaccharide derivatives containing 4,6-*O*-benzylidene acetal and anomeric β-(1,2,3)-triazole functional groups. In addition to the triazole function, the phenyl group can lead to enhanced π-π interactions, therefore these new molecules may be more suitable for nonpolar organic solvents and aromatic solvents, and oils rather than polar solvents or aqueous mixture.

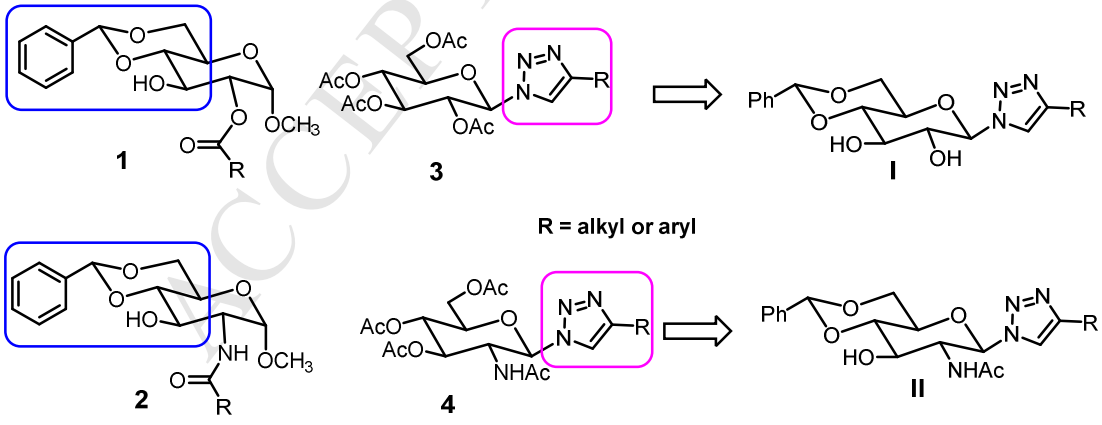


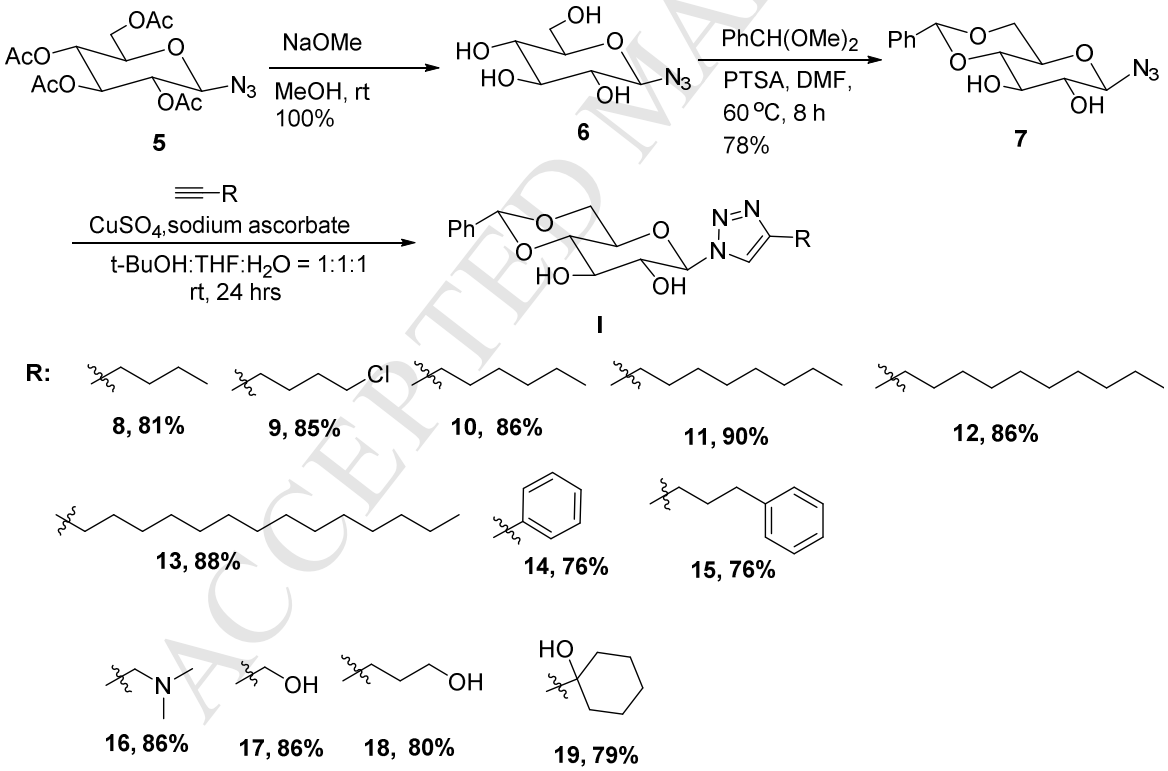
Figure 1. Structures of various protected D-glucose and D-glucosamine derivatives and the hybrid compounds **I** and **II**.

Results and Discussions:

In order to further explore the self-assembling properties of glycosyl triazole derivatives, we introduced 4,6-*O*-benzylediene acetal protecting group to the glycosyl triazoles to afford compounds with the general structures **I** and **II**. As mentioned earlier, the phenyl group is expected to enhance π-π interactions and perhaps enhance gelation tendencies for aromatic solvents. As shown in Schemes 1 and 2, we synthesized a series of triazole derivatives with the general structures of **I** and **II** from the corresponding azido peracetate of D-glucose and D-glucosamine (**5** and **20**). The selection of R group was based on our previous findings of effective gelators. The headgroup compound **7** was synthesized by treating glycosyl azide **5** with sodium methoxide in methanol, followed by protection with benzylidene acetal protective group. Then terminal alkynes with different functional groups were selected for the click reaction using copper sulfate and sodium L-ascorbate as the catalyst.[58-61] A series of new triazole derivatives **8-19** with the general structure **I** were then obtained in good yields.

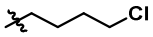
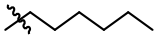
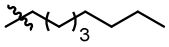
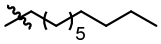
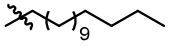
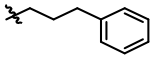
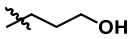
After these compounds were synthesized, their gelation properties in several solvents were tested and the gelation results are shown in Table 1. Besides the solvents listed in the table, we also analyzed hexane and THF, all compounds were insoluble in hexane, and all were soluble in THF except **16**, which was insoluble. All gels obtained were opaque except toluene gels, which were translucent. For the D-glucose triazole derivatives, the 4-triazolyl alkyl derivatives are generally more effective gelators than the derivatives with polar substituents. The n-butyl analog **8** formed stable gels in isopropanol, pump oil and unstable gels in toluene and engine oil. The chlorobutyl analog **9** formed gels in ethanol/water mixture and DMSO/water mixture. As the chain length increases, the compounds are more effective for oils. The hexyl derivative **10** was the most

efficient among these gelators, forming a gel in engine oil at 6.7 mg/mL concentration. The octyl analog **11** was the most versatile gelator, forming gels in six of the tested solvents, including isopropanol, ethanol/water, and DMSO/water mixtures. When the alkyl chains are longer (>8 carbons), the compounds are no longer effective gelators for the tested solvents. D-glycosyl triazole **15** containing a phenyl group with an alkyl spacer can form gels in DMSO/water mixtures. However, the hydroxyl bearing triazole analogues **17-19** didn't form gels in any of the tested solvents, possibly because the systems are too polar to function as a gelator, they are more soluble for polar organic solvents. In general, these series of derivatives **I** are less effective comparing to their peracetylated precursors **3**. However, we were pleased to find that all of the alkyl triazole derivatives **8**, **10-13** were effective gelators for pump oil.



Scheme 1. Synthesis of benzylidene acetal protected β-triazolyl glucosides **8-19**.

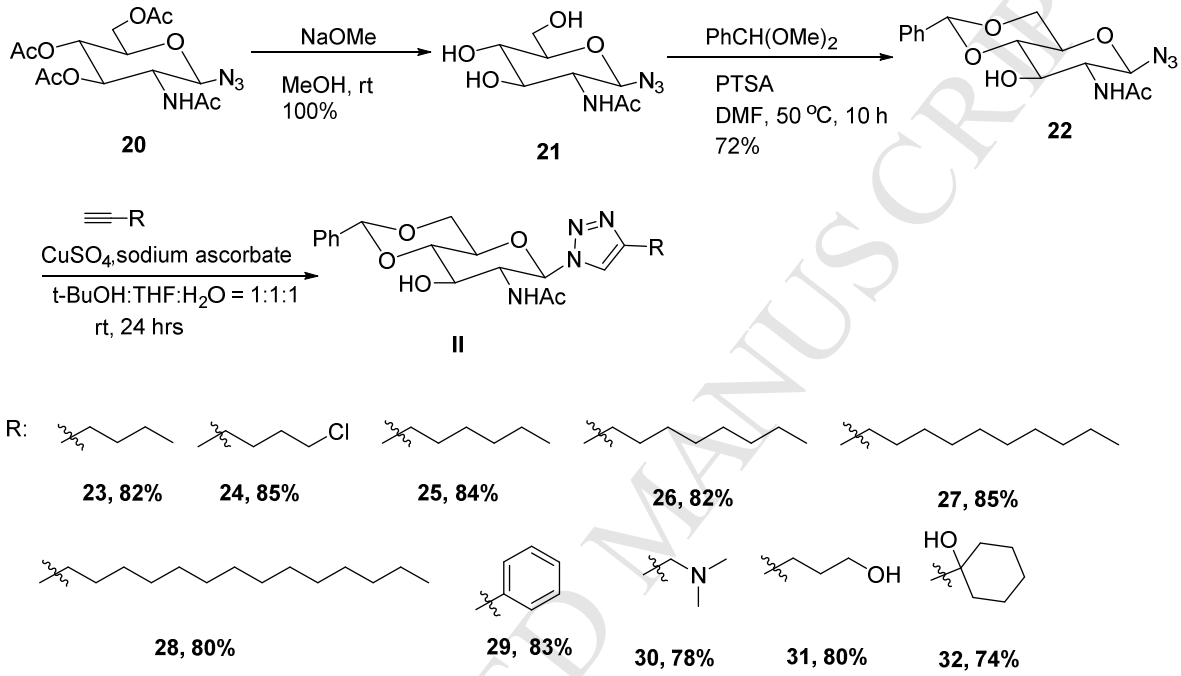
Table 1. Gelation test results of the partially protected D-glucosyl triazole derivatives **I**.

Compound	Structure R=	Pump oil	Engine oil	Toluene	i-PrOH	EtOH	EG	EtOH:H_2O (1:2)	DMSO:H_2O (1:2)	H_2O
8		G20	UG	UG	G 20	S	S	P	P	P
9		S	S	P	P	P	S	G10	G10	I
10		G10	G 6.7	P	P	S	S	P	G 6.7	I
11		G20	G 20	P	G 20	S	UG	G10	G 20	I
12		G20	I	P	S	S	S	P	I	I
13		G10	UG	P	P	P	P	P	I	I
14		I	I	I	P	S	S	P	S	I
15		UG	P	P	P	P	S	P	G 6.7	I
16		I	S	UG	S	S	S	S	S	P
17		I	I	I	P	S	S	S	S	S
18		P	I	I	S	S	S	P	P	I
19		I	I	I	S	S	S	S	S	p

All compounds were tested starting from 20 mg/mL. G, stable gel at room temperature, the number is minimum gelation concentration (MGC) in mg/mL; UG, partial gel or unstable gel, the concentration is 20 mg/mL unless otherwise specified. P, precipitation; S, soluble; I, insoluble.

Previously we have shown that the peracetylated glycosyl triazole derivatives from glucosamine were also effective gelators.[52] To probe the effect of changing protective groups, here we have synthesized the 4,6-O-benzylidene acetal protected glycosyl triazole derivatives **II**. As shown in

Scheme 2, using the same alkynes as in the synthesis of glycosyl triazoles **I**, the derivatives **II** were synthesized. Next their gelation properties in several solvents were tested, the results are shown in Table 2. Besides the solvents shown in Table 2, we also found that at 20mg/mL, these glucosamine derivatives were insoluble in hexane, but soluble in THF and ethylene glycol (EG).

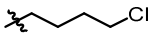
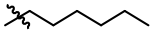
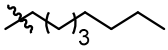
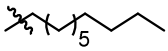
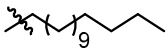
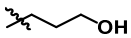


Scheme 2. Synthesis of bezylidene acetal protected β-triazolyl glycosides **23-32**.

For the D-glucosamine based triazoles **23-32**, in contrast to the ester series **I**, these compounds were considerably less effective as organogelators. The hexyl and octyl derivatives were the most efficient gelators in this series; forming gels in toluene, ethanol/water and DMSO/water mixtures. The compounds **II** were effective gelators for toluene when the triazolyl-4-substituents were aliphatic or phenyl; the shorter alkyl chain derivatives were effective gelators towards aqueous mixtures of DMSO and ethanol. It is interesting to observe that none of these glucosamine triazole compounds were effective for oils. The gels were typically opaque while some of them were clear gels. The representative gels are shown in Figure 2. In general, the D-

glucosamine triazole series **II** are less likely to function as gelators in comparison to the benzylidene acetal glucosamine series **2** and the peracetylated glycosyl β-triazole derivatives **4**.

Table 2. Gelation properties of the triazole derivatives (**II**) synthesized from N-acetyl D-glucosamine

No.	Structure R=	Pump oil	Engine oil	Toluene	i-PrOH	EtOH	EtOH: H_2O (1:2)	DMSO: H_2O (1:2)	H_2O
23		I	I	I	S	S	UG20 $_O$	G12 $_O$	I
24		I	I	I	S	S	S	S	I
25		I	I	G 20 $_C$	S	S	G 5.0 $_O$	G 4.0 $_O$	I
26		I	I	G 10 $_C$	S	S	G 6.7 $_O$	G 3.3 $_O$	I
27		I	I	G 20 $_C$	S	S	P	P	I
28		I	I	S	S	S	P	P	I
29		I	I	G 20 $_T$	I	P	I	I	I
30		I	I	I	S	S	S	S	S
31		I	I	I	S	S	S	S	S
32		I	I	P	S	S	S	S	S

All compounds were tested starting from 20 mg/mL. G, stable gel at room temperature, the numbers are MGCs in mg/mL; UG, partial gel or unstable gel; P, precipitation; S, soluble; I, insoluble. The subscribed letters denote the gel appearances: C, clear or transparent; T, translucent; O, opaque.

(a) (b) (c)

Figure 2. Gel photos for a) compound **9** in EtOH:H_2O (v/v 1:2) at 10 mg/mL; b) compound **25** in DMSO:H_2O (v/v 1:2) at 4 mg/mL; c) compound **26** in EtOH:H_2O (v/v 1:2) at 6.7 mg/mL.

Next we characterized the gels formed by compounds **9**, **25**, and **26** using an optical microscope. As shown in Figure 3, in EtOH:H_2O (v/v 1:2), compound **9** formed long thin fibers as the major morphology together with certain areas that were semi crystalline (left side of the image, Fig. 3a). It is possible that the thinner fibers or wires formed rapidly without reaching equilibrium and the larger tubules were composed of thinner tubes rearranged to form clusters. In DMSO:H_2O (v/v 1:2) the gel formed by compound **9** showed uniform fibrous morphology (Fig. 3b). The glucosamine derivative **25** in EtOH:H_2O (v/v 1:2) mixture formed long fibers in uniform diameter (~1 µm) and up to 200 µm in length (Fig. 3c). And it formed long and narrower fibrous structures in DMSO:H_2O (v/v 1:2) (Fig. 3d), the diameter was about 0.5 µm and up to 200 µm in length, the fibers were more interconnected and curved. For both solvent systems, the fibers were more uniform and didn't appear to have different domains of morphology. The EtOH:H_2O (v/v 1:2) gel of compound **11** showed uniform birefringent fibrous networks (Fig. 3e). The compound **26** formed a mixed morphology similarly to that of compound **9**, the majority of the aggregates appeared liquid crystalline and birefringent sheets or ribbons (Fig. 3f).

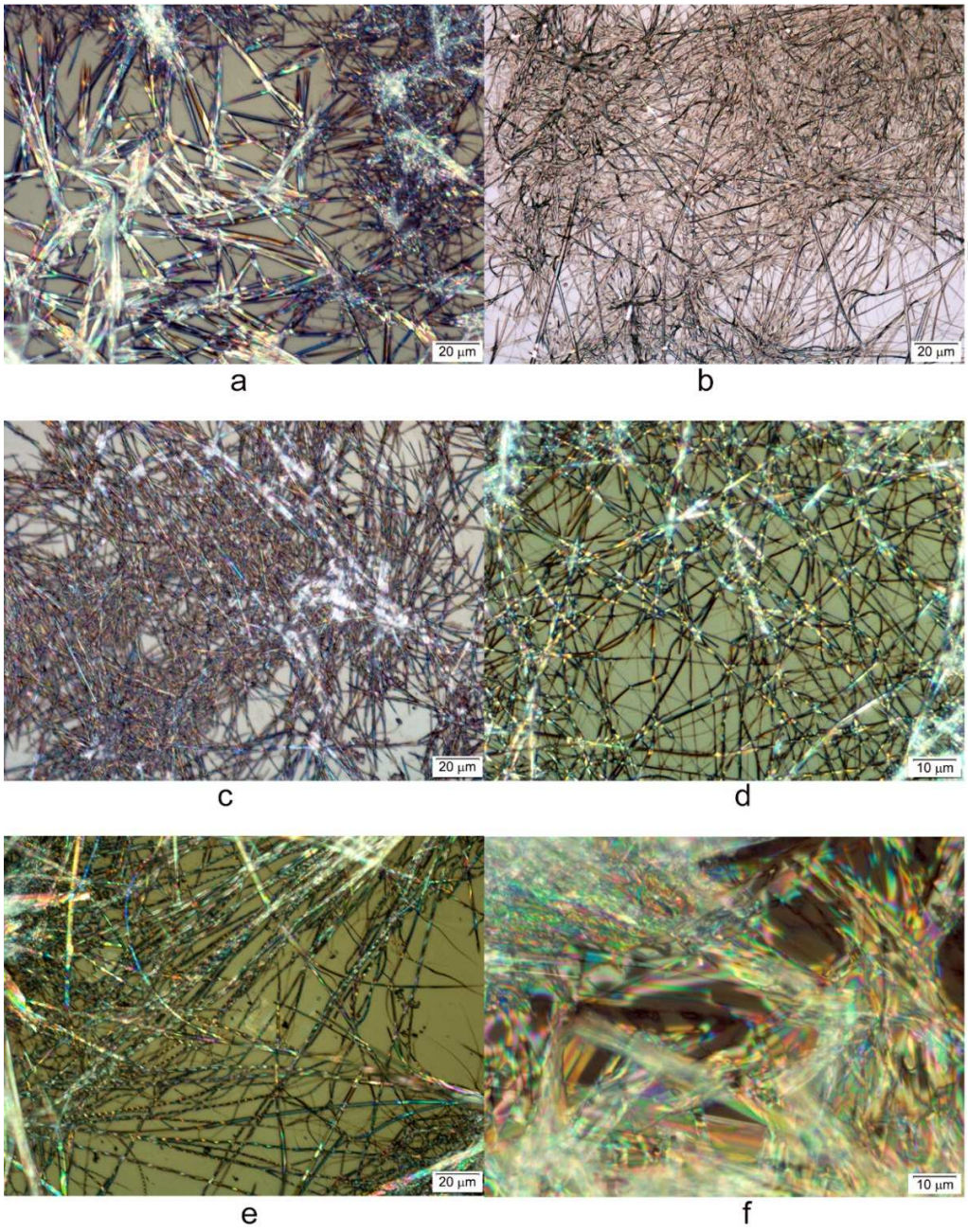


Figure 3. Optical micrographs of dried gels formed by compound **9**, **25**, **11** and **26**; a) compound **9** in EtOH:H_2O (v/v 1:2) at 10.0 mg/mL; b) compound **9** in DMSO:H_2O (v/v 1:2) at 10.0 mg/mL; c) compound **25** in EtOH:H_2O (v/v 1:2) at 5.0 mg/mL; d) compound **25** in DMSO:H_2O (v/v 1:2) at 4.0 mg/mL; e) compound **11** in EtOH:H_2O (v/v 1:2) at 10.0 mg/mL; f) compound **26** in EtOH:H_2O (v/v 1:2) at 6.7 mg/mL.

Next we analyzed the rheological properties of the gels formed by several compounds in DMSO:H_2O (v/v 1:2). The storage modulus G' and loss modulus G'' at different angular frequencies of the gels formed by compounds **9**, **15**, **25**, and **26** were shown in Figure 4. The storage moduli for all four compounds were greater than their loss moduli in all frequency ranges, with compound **9** having the largest storage moduli in the four, the gels were more stable than the others.

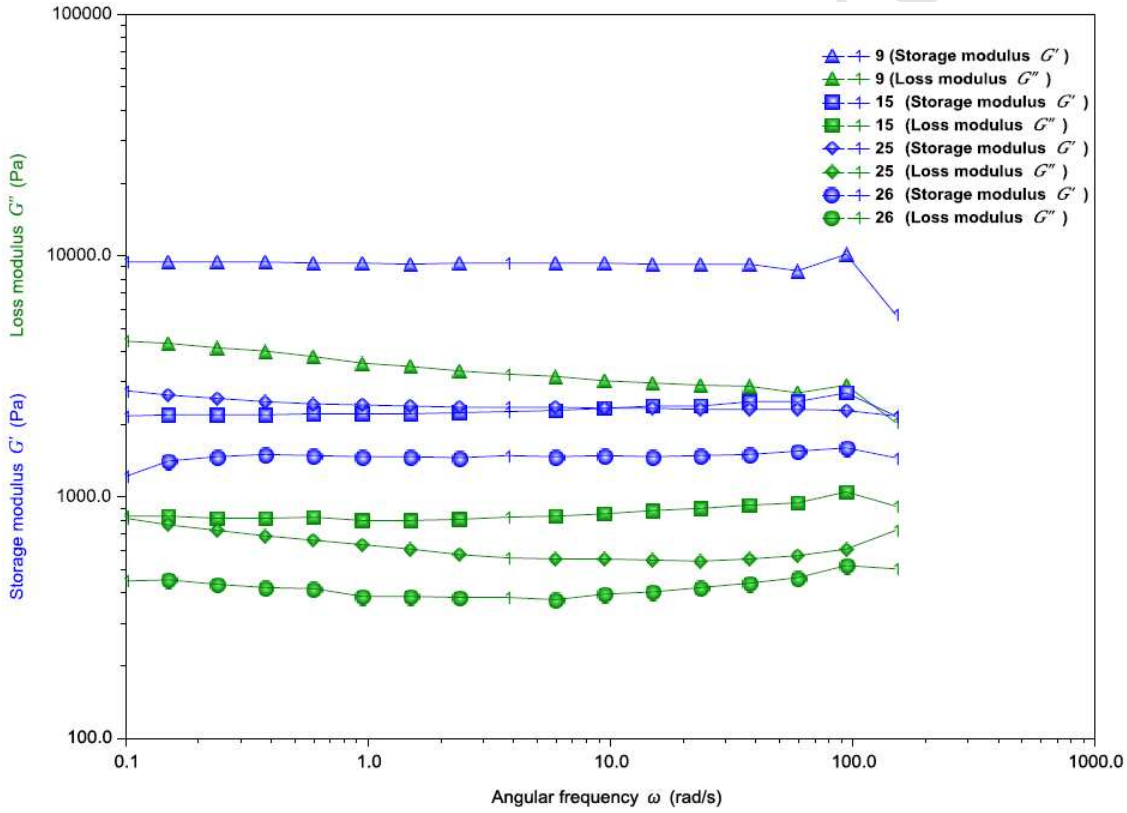
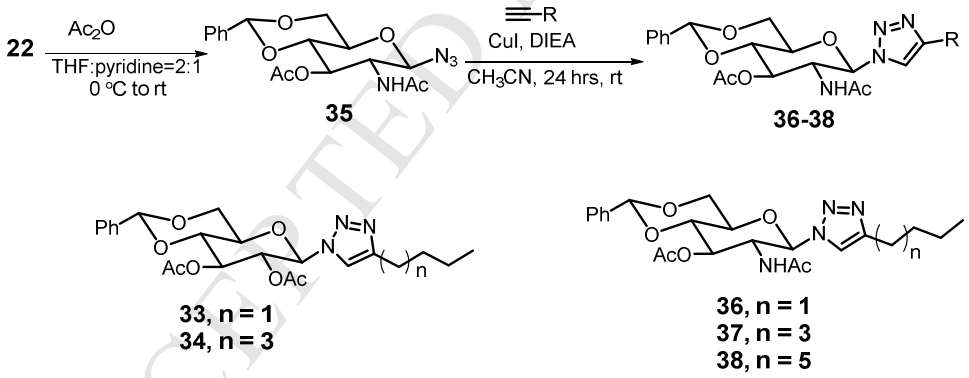


Figure 4. The rheological measurement of the gels in DMSO:H_2O (v/v 1:2) formed by **9** at 10 mg/mL, **15** at 6.7 mg/mL, **25** at 4.0 mg/mL, and **26** at 3.3 mg/mL concentrations, the applied strain was 5% for all samples.

Among the different classes of glycosyl β-triazole derivatives, some of the benzylidene acetal derivatives **I** and **II** were able to form gels. In order to understand the effect of protective groups towards the self-assembling properties, several effective gelators in each series were selected to prepare the fully protected peracetate of the benzylidene acetal. Full acetylation of the corresponding glucose derivatives **8** and **10** afforded compounds **33** and **34** (Scheme 3). Compounds **36-38** are the acetates of the glucosamine based gelators **23**, **25**, and **26**. They can be synthesized by direct acetylation of the precursors or from the azidosugar **35**. As shown in Scheme 3, they were prepared by acetylation of the azide headgroup **22** first and followed by the click reaction. Five fully protected compounds (**33-34, 36-38**) were synthesized and tested and the results are shown in Table 3, interestingly most of the acetylated compounds lost gelation tendencies.



Scheme 3. Synthesis of the acetylated β-triazolyl glycosides **36-38**.

Table 3. Gelation properties of the acetylated β-triazolyl glycosides

No.	Precursor	Pump oil	Engine oil	Toluene	i-PrOH	EtOH	EtOH: H_2O (1:2)	DMSO: H_2O (1:2)	DCM
33	**8**	I	S	S	I	I	I	I	S
34	**10**	G 20	UG 20	S	P	P	I	I	S
36	**23**	I	I	P	I	P	I	I	I
37	**25**	I	P	P	P	P	I	I	I
38	**26**	S	P	P	P	I	I	I	P

All compounds were tested starting from 20 mg/mL. G, stable gel at room temperature, the numbers are MGC in mg/mL; UG, partial gel or unstable gel; P, precipitation; S, soluble; I, insoluble. All were insoluble in hexane, and water.

As we have seen before that the 3-hydroxy group on the sugar ring plays an important role in forming gels.[50] Here we noticed the same effect, after blocking the 3-OH position, the gelation tendency diminished or disappeared. Compound **25** was an effective gelator for toluene, ethanol/water (1:2) mixture and DMSO/water (1:2) mixture; but after introducing the acetyl group at the 3-OH position, the resulting compound **37** no longer formed gels in these tested solvents. This indicated that the 3-OH group was important towards gelation, the hydrogen bonding donor is critical for effective gelation for this class of compounds. The same trend was observed for other analogs as well. The diacetate of the glucosyl triazole derivatives **8** and **10** give compounds **33** and **34**, which exhibited diminished gelation tendencies. And for the glucosamine derivatives, all three derivatives lost gelation properties. This response towards simple acetylation could be useful in application of stimuli-responsive gelation either with a base or an esterase to cleave the acetate, which will be studied in future research.

We rationalized the observation using ^{1}H NMR spectroscopy studies at different temperatures for compound **25** and its acetate **37**. The ^{1}H NMR spectra at different temperatures for compound **25** are shown in Figure 5. Upon increasing temperature from 30 °C to 60 °C, the triazole aromatic C-H chemical shift moved upfield noticeably from 7.91 to 7.86 ppm (Δ 0.05 ppm); the amide signal changed upfield from 7.93 to 7.81 ppm (Δ 0.12 ppm). And the proton of the 3-OH signal shifted from 5.58 to 5.43 ppm (Δ 0.15 ppm); this was the largest change of the chemical shift which indicates that hydrogen bonding using the free 3-hydroxyl group is very important for this system and contributes significantly towards gelation. The amide hydrogen bond is also an important contributing factor towards gelator self-assembling process. The anomeric hydrogen showed a small downfield change upon increasing temperature. This slight downfield change can be caused by enhanced intramolecular hydrogen bonding at higher temperature, though the intermolecular hydrogen bonding is weakened.

After forming the acetate which blocks the hydrogen bonding donor at 3-position, the triazole C-H signal in compound **37** changed from 8.00 to 7.93 (Δ 0.07 ppm). While the amide signal changed from 8.06 to 7.92 ppm (Δ 0.14 ppm) upon increasing temperature; these are similar or a little stronger than those for compound **25**, indicating that after acetylation, the amide and triazole functional groups didn't lose their intermolecular interactions. Interestingly, the anomeric proton in this case didn't show meaningful chemical shift change, and the 3-CH changed slightly downfield from 5.39 to 5.41 ppm. The NMR spectra indicated that the amide hydrogen bonding, triazole and phenyl π-π interactions were important intermolecular forces in molecular self-assembly. But these stronger interactions didn't induce gelation necessarily. The variable temperature study of this model system allows us to understand the effect of different

derivatization to the sugar template. Moreover, a delicate balance of hydrophilicity and hydrophobicity, intermolecular forces are necessary for effective gelation. Too strong interactions will result in precipitation or crystallization but poor gelation.

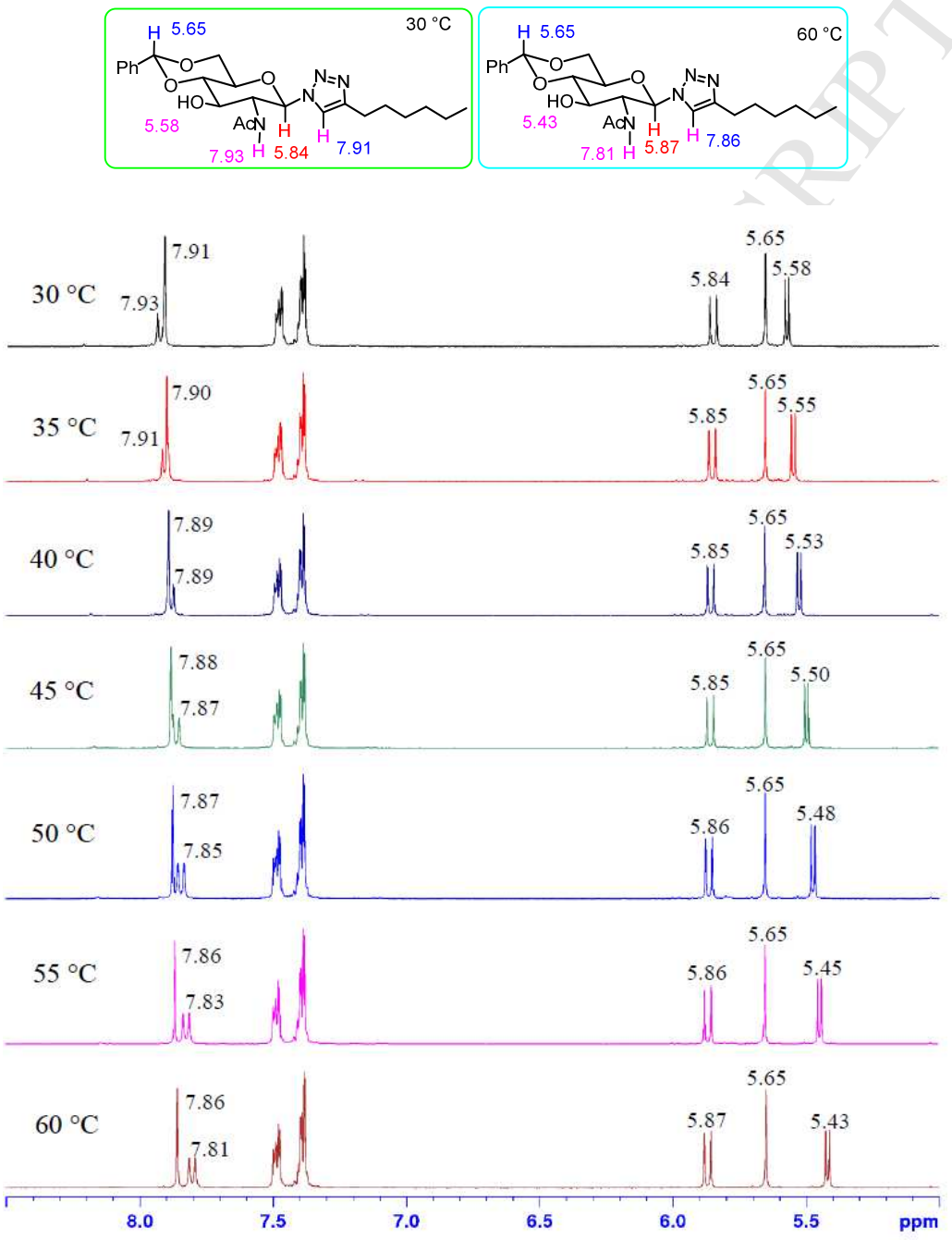


Figure 5. The ^{1}H NMR spectra of compound **25** from 30 °C to 60 °C in d_6-DMSO (10 mg/mL).

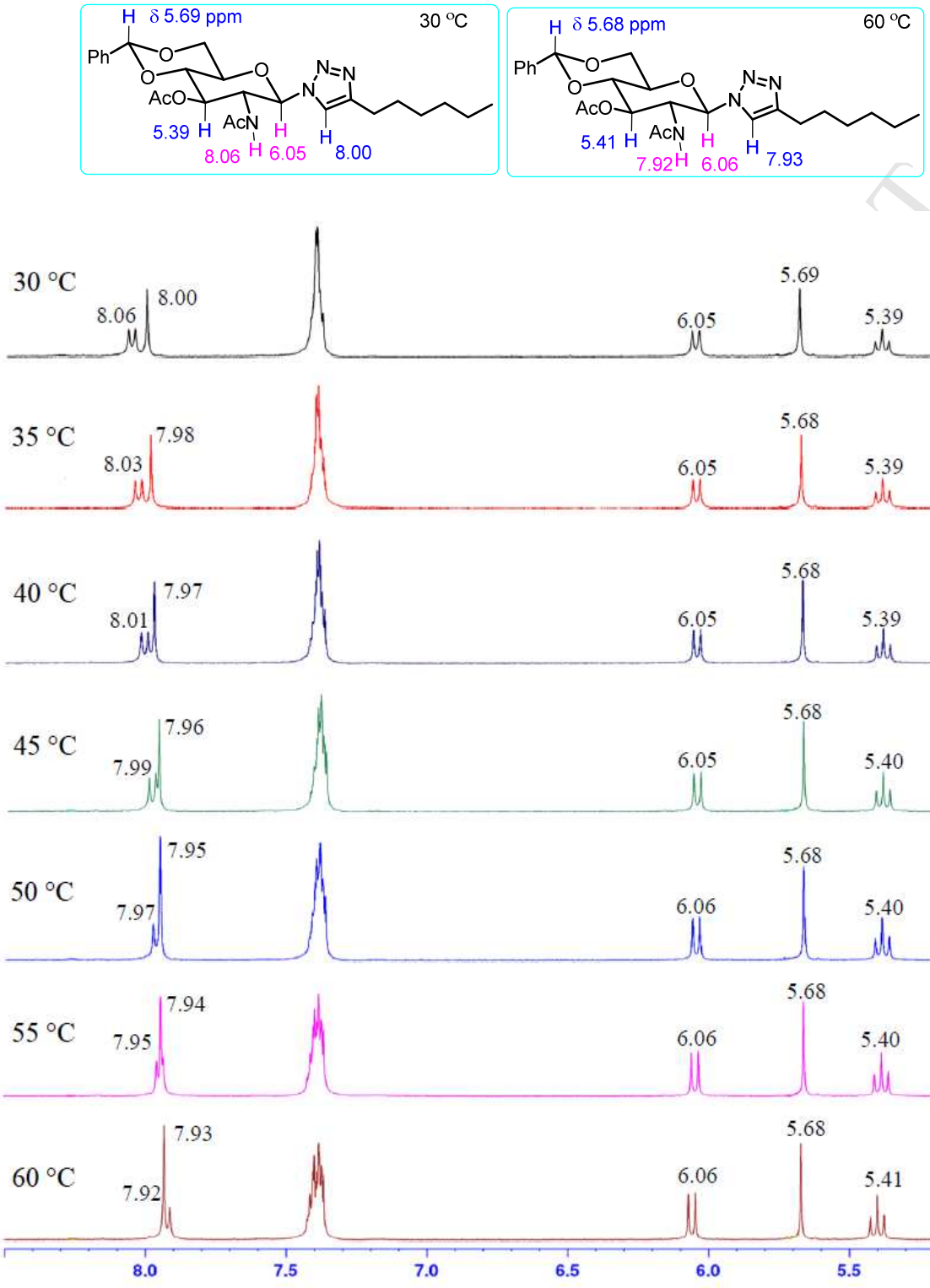


Figure 6. The ^{1}H NMR spectra of compound **37** from 30 °C to 60 °C in d_6-DMSO (10 mg/mL).

We carried out additional temperature dependent experiments by adding D_2O to DMSO-*d*6 for compounds **9** and **25**. This solvent combination mimics the gelation solvents and also allows us to observe the change of exchangeable protons after adding D_2O.[62] We acquired the NMR spectrum of the compounds in pure DMSO-*d*6, then D_2O was added to the NMR tube and the solvent was mixed through vortex, the 3-OH and the amide signals disappeared, at higher temperatures, only the water signals changed significantly and other signals didn't change much. These are shown in the Supporting Information-I Figures S9 and S10. In addition, we also carried out the time dependent NMR study for compound **25** after adding D_2O and acquire the spectrum right away. The time dependence ^1H NMR spectra are shown in Figure 7. As what to be expected, the proton signal of 3-OH disappeared upon addition of D_2O right away, but the amide signal gradually exchanged with deuterium within half an hour. The rate of the exchange with deuterium for amide functional group is fairly fast (SI-I Figure S10c and Table S5). Addition of D_2O also led to chemical shift changes for several signals including the NH and anomeric proton. The most significant change observed was for the water absorptions, which shifted from 3.30 to 3. 90 ppm after equilibrium. These results indicated that both the hydroxyl group and the amide functional group are involved in intermolecular hydrogen bonding which leads to the formation of molecular assembly and gelation.

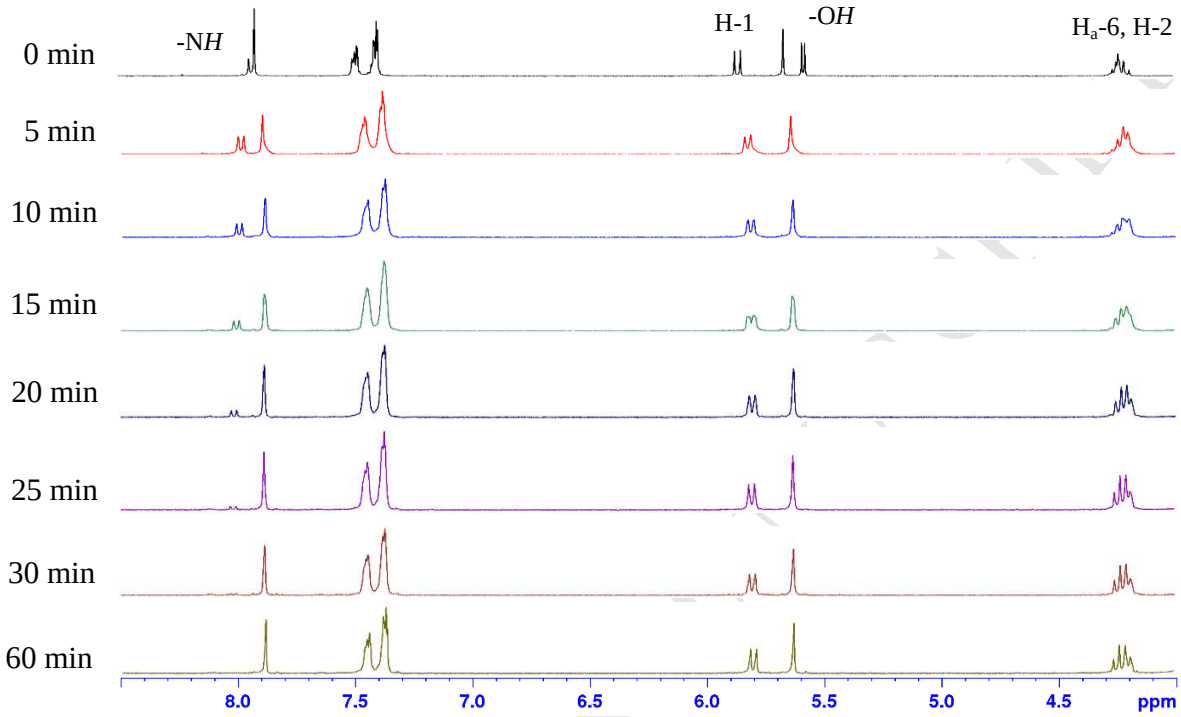


Figure 7. Time dependent ^{1}H NMR spectra of compound **25** (1.6 mg in 0.40 mL d_6-DMSO) after addition of 0.10 mL D_2O to the sample. The NMR spectra were all acquired at 30 °C.

FTIR spectroscopy can shed some light on the structural information of functional groups and help us to understand the structures in the gel phase.[63,64] Therefore we acquired the FTIR spectra for triazole derivative **25** in its solid form and the gel in ethanol water mixture. The expanded regions for the FTIR spectra are shown in Figure 8. In the gel phase, a new peak at 3375 cm^{-1} was detected, which can be attributed to enhanced intermolecular hydrogen bonding between the free 3-OH with other gelators and solvents, this could be the amide NH stretching vibration too.

An enhanced signal at 3062 cm^{-1} in the gel phase than the solid indicates that the gel state has stronger aryl and triazole CH stretch vibration, possibly due to stronger π-π interactions at the gel phase. The C-H stretch signals in 2924, 2869, and 2854 cm^{-1} have small red shifts in the gel phase, this implies that the C-H stretching are weaker (lower in energy) at the gel phase, possibly due to the stronger hydrophobic interactions in the gel. The amide I band (the C=O stretching band) in the solid form absorbed at 1661 cm-1, and the amide II band (the N-H bend) frequency was 1536 cm^{-1}. In the gel state, the amide I band shifted to 1668 cm^{-1} and the amide II shifted to 1530 cm^{-1} with stronger relative intensities. The triazole C=C stretch signal appeared at 1643 $cm^{-1}$for the gel state, which was also stronger than the signal in the pure solid, this indicated stronger intermolecular triazole packing in the gel state. Likewise, the aryl carbon-carbon stretch shifted from 1454 cm^{-1} in solid to 1458 cm^{-1} in the gel state with stronger intensity. The FTIR analysis clearly indicated that hydrogen bonding and other intermolecular forces are important in the gelation process. We also carried out the FTIR experiments for the gel of compound **10** in DMSO:water (v/v 1:2) at 6.7 mg/mL, the DMSO water gel showed less changes in their solid and gel phase comparing to the system discussed above. The FTIR spectra of several gels formed by compounds **9**, **10**, **11**, **25** and **26** are shown in Supporting Information I Figures S11-S20.

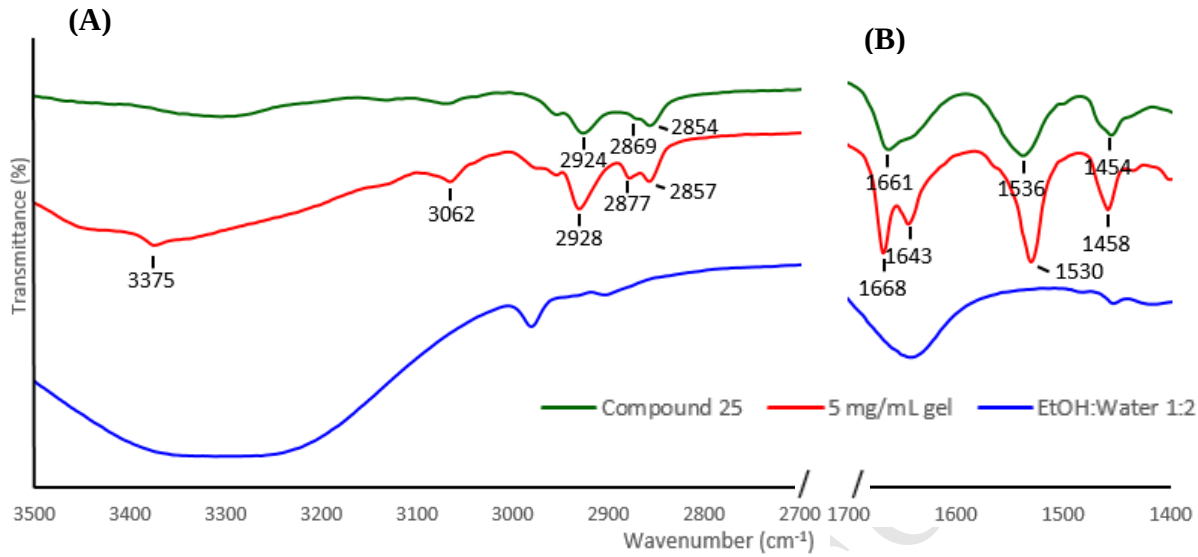
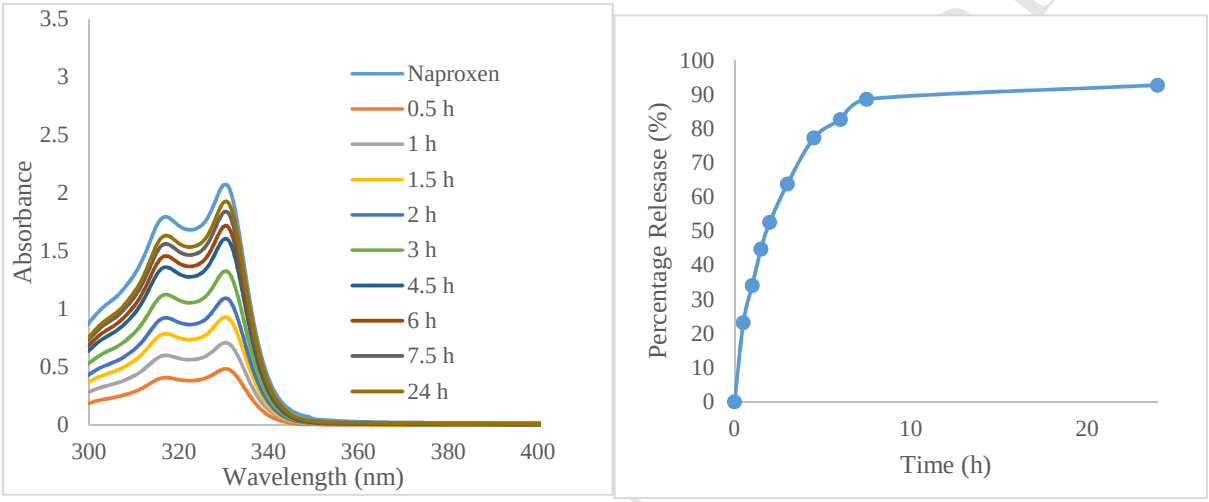


Figure 8. FTIR spectra for compound **25** in 2700-3500 cm^{-1} and 1400-1700 cm^{-1} (expanded regions). The green curve corresponds to the solid form, the red curve corresponds to the gel form of **25** in EtOH:H_2O (v/v 1:2) at 5.0 mg/mL, and the blue curve is the solvent standard of EtOH:H_2O (v/v 1:2).

For potential drug delivery or other applications using the gel matrix, it is more desirable if the gelator can form gels in water or with minimum amount of DMSO. We tested the gelation properties of compounds **10** and **25** in different ratios of DMSO and water, the results are shown in supporting information Table S6. The glucosamine derivative **25** was able to form a stable gel in DMSO:H_2O at 1:5 ratio. We selected this compound and formed a co-gel with naproxen in DMSO:H_2O (v/v 1:5) at 6.7 mg/mL and analyzed the sustained release of naproxen from the gel phase to water phase, the results are shown in Figure 9. Naproxen was released rapidly to the aqueous phase, in 2 hours about half of the naproxen was detected in the aqueous phase and it was fully released to the water phase within a day. With different gelator concentrations, we

expected that the timed release of naproxen could be controlled for longer or shorter duration. This compound could be used to encapsulate other drug compounds and may be able to form more compatible and stable co-gels at different conditions, from which the drug will be released more slowly.



a b

Figure 9. Release of naproxen from gel to aqueous phase. a) UV spectra of the naproxen timed release, the gel was formed by 2.0 mg of compound **25** in 0.3 mL DMSO:H_2O (v/v 1:5) with 1.0 mg of naproxen, then 3 mL of water was added on top of the gel; naproxen control was prepared by dissolving 1.0 mg naproxen in 3 mL of water (pH 7); b) Absorbance at 330 nm at different times versus the standard was used to calculate the % release.

Conclusions:

We have synthesized and studied a series of β-triazolyl glycoside of 4,6-*O*-benzylidene acetal protected D-glucose and D-glucosamine systematically. A few low molecular weight organogelators were obtained and the gels were characterized using optical microscopy, rheology

and FTIR spectroscopy. The D-glucose derivatives are more effective gelators for organic solvents especially for pump oil and engine oil, whereas the D-glucosamine derivatives are less effective for oils but more effective towards polar solvents and their aqueous mixtures. However, the presence of the 4,6-O-benzylidene acetal functional group seems to weaken the gelation tendencies for some triazolyl glycosides in comparisons to the corresponding tetra-acetyl glycosyl triazoles perhaps due to the structural rigidity of the bicyclic ring system. A few effective gelators were further acetylated and the resulting fully protected diacetates lost gelation abilities. We noticed that the hydrogen bonding of the 3-OH group plays a critical role in the observed gelation properties. ^{1}H NMR spectra at different temperatures for compound **25** and its acetate **37** revealed the importance of the free 3-hydroxyl group in the molecular self-assembly and gelation process. Furthermore, we analyzed the FTIR spectra for compound **25** in its solid and gel states, new absorption signals were observed for the gel phase, which supported the NMR study results. Compound **25** was also used in a test for naproxen co-gel formation and the release of naproxen from the gel matrix was monitored by UV-vis spectroscopy. We expect that further structural optimization of these derivatives could lead to more effective gelators or gelators that are compatible to different drug molecules for encapsulation and sustained release. The general trend of these compounds can be used to design systems with or without the desire to form stable gels, which have implications in biological or materials applications.

Experimental sections

General method and materials: 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 spectrometers in DMSO-d_6 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. FTIR experiments were conducted using liquid or solid samples directly. The molecular mass was measured using LCMS on an Agilent 6120B Single Quad Mass Spectrometer and LC1260 system.

Optical Microscopy: A small amount of the gels was placed on a clean glass slide and this was observed under an Olympus BX60M optical microscope and the Olympus DP73-1-51 high performance 17MP digital camera with pixel shifting and Peltier cooled. The imaging software for image capturing was CellSens 1.11. For aqueous DMSO mixtures, the gel was left air dried for a day or so, for other solvents the slides were observed directly.

Gel Testing: About 2.0 mg of dried compound was placed in a one dram glass vial and the corresponding solvent was added to obtain a concentration of 20 mg/mL. The mixture was then heated until the solid was fully dissolved, sometimes sonication was needed to dissolve the sample, and then the solution was allowed to cool to room temperature and left standing for 30 minutes. If a stable gel formed (observed by inverting the vial), it was then serially diluted till

the minimum gelation concentration (MGC), which is the concentration prior to unstable gelation, was obtained.

Rheological Analyses: The rheological behavior of the gel was investigated with an HR-2 Discovery hybrid rheometer from TA Instruments with TRIOS software. A sample (approximately 1mL of the gel) was placed on the steel plate of the rheometer. The cone geometry is a 25 mm Peltier plate with a gap of 100 μm. The experimental temperature was 25 °C, and the sample was subjected to amplitude sweep for oscillation strain from 0.125 to 10%. A frequency sweep was then performed for the sample in the range of 0.1 to 150 rad/s for the angular frequency. The results were expressed as the storage modulus (G') and loss modulus (G'') as a function of angular frequency.

FTIR Spectroscopy: FTIR measurements were performed on a Bruker ALPHA Platinum ATR FTIR Spectrometer, the operating software is OPUS. The absorption spectra of all samples were obtained at room temperature in the range of 400-4000 cm^{-1}.

Liquid chromatography-mass spectrometer (LC-MS) conditions: The molecular mass acquisition was performed on a liquid chromatography-mass spectrometer system which consists of an Agilent 1260 Infinity LC system coupled to a G6120B single quadrupole mass spectrometer with an atmospheric pressure ionization electrospray (API-ES). The analytical column is an Agilent poroshell 120 EC-C18 4.6 mm × 50 mm column with 2.7 μm particle size. The mobile phase is 0.1% formic acid in acetonitrile/water (70/30, v/v). Ejection volume is 5 μL. Total runtime is 8 min. The flow rate is 0.40 mL/min and the column temperature is set at 25 °C.

Wavelength of diode-array detector (DAD) is 254 nm. Data was collected and processed using Agilent OpenLAB CDS ChemStation (Version C.01.05). The ESI spray voltage was set at 4000 V. The source temperature is 350 °C. The nebulizer gas setting is 35. Range of mass spectrometer detector is set from 0 to 2000 Dalton.

Naproxen trapping and release: A gel was prepared in a one dram via using 2.0 mg of compound **25** and 1.0 mg of naproxen sodium and 0.3 mL DMSO:H_2O (v1:5), after a stable gel was formed and the gel was left undisturbed for 2 hours, 3 mL of water at pH 7 was added to the top of the gel carefully. Naproxen release from the gel was monitored by UV absorption at certain time by transferring the supernatant with a pipet to a cuvette, after each measurement the aqueous phase was carefully transferred back to the vial and placed on top of the gel again till the next measurement. The UV spectra of the pure naproxen and pure gelator in the test solvent system were also recorded.

Synthesis of sugar headgroup azide 7:

The headgroup azide **7** was synthesized following literature method with slight modifications using D-glucose as the starting material.[65] Compound **5** (3.80 g, 10.15 mmol, 1 equiv) was dissolved in MeOH (15 mL) and NaOMe (273 mg, 5.08 mmol, 0.5 equiv) were added to 50 mL round bottom flask. The reaction mixture was stirred for 12 hours at rt, neutralized with Amberlite IR 120 hydrogen form, filtered, concentrated and vacuum drying overnight to give 2.08 g (10.15 mmol, quantitative) brown semi-solid as the desired product. Compound **6** was co-distilled with toluene (3 x 10 mL) and directly used for the next step without further purification. Toluene treated compound **6** (2.08 g, 10.15 mmol, 1 equiv), dimethyl benzaldehyde acetal (1.83

mL, 12.18 mmol, 1.2 equiv), PTSA monohydrate (196 mg, 1.02 mmol, 0.1 equiv) were added in the given order and followed by adding 10 mL of DMF (anhydrous) as the solvent. The resulting mixture was stirred for 8 hours at 60 °C. After neutralizing the reaction mixture by adding $NaHCO_3$ (170 mg, 2.04 mmol, 0.2 equiv), DMF was removed by the rotavap and workup was performed using DCM (3x40 mL) /water (20 mL) to give the crude product, which was purified by column chromatography using eluent from 1% MeOH/DCM to 5% MeOH/DCM to give white solid (2.32 g, 7.91 mmol, 78% over two steps) as the desired product (R_f = 0.3 in 3% MeOH/DCM). mp 136-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.46 (m, 2H), 7.41-7.35 (m, 3H), 5.54 (s, 1H), 4.67 (d, J = 8.6 Hz, 1H), 4.38 (dd, J = 10.4 Hz, 4.3 Hz, 1H), 3.85-3.75 (m, 2H), 3.59-3.51 (m, 2H), 3.44 (t, J = 8.6 Hz, 1H), 3.00-2.45 (br s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 136.7, 129.4, 128.4, 126.3, 102.0, 90.6, 80.1, 74.1, 73.5, 68.41, 68.36.

General procedure for the synthesis of triazoles 8-19:

To a scintillation vial, azide **7** (100 mg, 0.340 mmol, 1 equiv) and alkyne (0.400 mmol, 1.2 equiv) were dissolved in the 6 mL of solvent mixture of THF: H_2O: *t*-BuOH (v/v 1:1:1). $CuSO_4$ (11.1 mg, 0.068 mmol, 0.2 equiv) and L-ascorbic acid sodium salt (27.2 mg, 0.136 mmol, 0.4 equiv) were added to the reaction mixture. Reaction was stirred for 24 hours at rt. Solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography to afford the desired triazole product **8-19**.

Synthesis of compound 8:

1-Hexyne (0.047 mL, 0.410 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (103 mg, 81%) as the desired product (R_f = 0.33 in 5% MeOH/DCM); mp 214-216 °C; ^{1}H NMR (400 MHz, $CDCl_3$+ one drop d_6-DMSO) δ 7.36 (s, 1H), 7.32-7.26 (m, 2H), 7.20-7.10 (m, 3H), 5.41 (d, *J* = 8.9 Hz, 1H, H-1), 5.34 (s, 1H, Ph-C*H*-), 4.12-4.09 (m, 1H, H-6_a), 3.86 (t, *J* = 8.9 Hz, 1H, H-2), 3.66 (t, *J* = 8.8 Hz, 1H, H-3), 3.59-3.42 (m, 3H, H-6_b, H-4, H-5), 2.49 (t, *J* = 7.7 Hz, 2H), 1.47-1.39 (m, 2H), 1.20-1.16 (m, 2H), 0.71 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + one drop d_6-DMSO) δ 147.5 (-HC=*C*-), 138.5, 128.6, 127.6, 125.9, 119.6 (-H*C*=C-), 101.3 (Ph-*C*H-), 87.5 (C-1), 79.7 (C-4), 73.3 (C-3), 72.8 (C-2), 68.7 (C-5), 67.7 (C-6), 30.8, 24.7, 21.7, 13.3; LC-MS (ESI+) calcd for $C_{19}H_{26}N_3O_5$ $[M + H]^+$ 376.2 found 376.2.

Synthesis of compound 9:

6-Chloro-1-hexyne (0.050 mL, 0.410 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (119 mg, 85%) as the desired product (R_f = 0.35 in 5% MeOH/DCM); mp 163-165 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.09 (s, 1H, -*H*C=C-), 7.50-7.45 (m, 2H), 7.42-7.36 (m, 3H), 5.70 (d, *J* = 9.2 Hz, 1H, H-1), 5.64-5.58 (m, 3H, Ph-C*H*-, 2-O*H*, 3-O*H*), 4.24-4.18 (m, 1H, H-6_a), 3.95-3.88 (m, 1H, H-2), 3.78-3.64 (m, 5H, H-5, H-6_b, H-3, -CH_2-Cl), 3.57 (t, *J* = 9.1 Hz, H-4), 2.67 (t, *J* = 7.1 Hz, 2H), 1.83-1.68 (m, 4H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 147.2 (-HC=*C*-), 136.8, 129.1, 128.1, 126.3, 120.2 (-H*C*=C-), 101.8 (Ph-*C*H-), 87.9 (C-1), 80.0 (C-4), 73.9 (C-3), 73.4 (C-2), 69.2 (C-5), 68.2 (C-6), 44.5 (-*C*H_2-Cl), 31.7, 26.3, 24.6; LC-MS (ESI+) calcd for $C_{19}H_{25}N_3O_5Cl$ $[M + H]^+$ 410.1 found 410.1.

Synthesis of compound 10:

1-Octyne (0.060 mL, 0.410 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (118 mg, 86%) as the desired product (R_f = 0.3 in 5% MeOH/DCM); mp 200-201 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + one drop d_6-DMSO) δ 7.49 (s, 1H, -*H*C=C-), 7.48-7.44 (m, 2H), 7.33-7.28 (m, 3H), 5.56 (d, *J* = 9.1 Hz, 1H, H-1), 5.52 (s, 1H, Ph-C*H*-), 4.31-4.25 (m, 1H, H-6$_a$), 4.09 (t, *J* = 8.9 Hz, 1H, H-2), 3.90 (t, *J* = 8.8 Hz, 1H, H-3), 3.77-3.61 (m, 3H, H-6$_b$, H-4, H-5), 2.66 (t, *J* = 7.8 Hz, 2H), 1.63-1.56 (m, 2H), 1.37-1.19 (m, 6H), 0.83 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + one drop d_6-DMSO) δ 148.1 (-HC=*C*-), 136.8, 129.1, 128.1, 126.3, 120.1 (-H*C*=C-), 101.8 (Ph-*C*H-), 87.8 (C-1), 79.9 (C-4), 73.8 (C-3), 73.3 (C-2), 69.2 (C-5), 68.1 (C-6), 31.4, 29.0, 28.8, 25.4, 22.4, 13.9. LC-MS (ESI+) calcd for $C_{21}H_{30}N_3O_5$ 404.2 $[M + H]^+$ found 404.2.

Synthesis of compound 11:

1-Decyne (0.072 mL, 0.410 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (132 mg, 90%) as the desired product (R_f = 0.34 in 5% MeOH/DCM); mp 206-207 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.05 (s, 1H, -*H*C=C-), 7.50-7.46 (m, 2H), 7.43-7.36 (m, 3H), 5.69 (d, *J* = 9.3 Hz, 1H, H-1), 5.63 (s, 1H, Ph-C*H*-), 5.61-5.58 (m, 2H, 2-O*H*, 3-O*H*), 4.23-4.18 (m, 1H, H-6$_a$), 3.96-3.88 (m, 1H, H-2), 3.78-3.64 (m, 3H, H-5, H-6$_b$, H-3), 3.57 (t, *J* = 9.1 Hz, 1H), 2.61 (t, *J* = 7.6 Hz, 2H), 1.63-1.54 (m, 2H), 1.38-1.19 (m, 10H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 147.0 (-HC=*C*-), 137.6, 128.8, 128.0, 126.3, 120.9 (-H*C*=C-), 100.7 (Ph-*C*H-), 87.4 (C-1), 80.1 (C-4), 73.2 (C-3), 72.7 (C-2), 68.4 (C-5), 67.5 (C-6), 31.2, 28.8, 28.7, 28.59, 28.56, 25.0, 22.0, 13.9. LC-MS (ESI+) calcd for $C_{23}H_{34}N_3O_5$ $[M + H]^+$ 432.2 found 432.2.

Synthesis of compound 12:

1-Dodecyne (0.088 mL, 0.410 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (136 mg, 86%) as the desired product (R_f = 0.3 in 5% MeOH/DCM); mp 212-214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.49 (m, 2H), 7.47 (s ,1H, -*H*C=C-), 7.42-7.33 (m, 3H), 5.57 (s, 1H, Ph-C*H*-), 5.52 (d, *J* = 8.9 Hz, 1H, H-1), 4.40-4.29 (m, 2H, H-6_a, H-2), 4.07-4.00 (t, *J* = 8.9 Hz, 1H, H-3), 3.83-3.67 (m, 3H, H-6_b, H-4, H-5), 2.67 (t, *J* = 7.7 Hz, 2H), 1.72-1.57 (m, 2H), 1.41-1.18 (m, 14H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6 (-HC=*C*-), 136.7, 129.4, 128.4, 126.3, 120.6 (-H*C*=C-), 102.0 (Ph-*C*H-), 87.8 (C-1), 79.9 (C-4), 73.7 (C-3), 73.2 (C-2), 69.3 (C-5), 68.3 (C-6), 31.9, 29.6, 29.5, 29.4, 29.31, 29.27, 29.2, 25.5, 22.7, 14.1; LC-MS (ESI+) calcd for $C_{25}H_{38}N_3O_5$ $[M + H]^+$ 460.3 found 460.3.

Synthesis of compound 13:

1-Hexadecyne (0.100 mL, 0.410 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (108 mg, 88%) as the desired product (R_f = 0.2 in 5% MeOH/DCM); mp 203-205 °C; ^{1}H NMR (400 MHz, $CDCl_3$, spectrum was taken at 55 °C) δ 7.54-7.50 (m, 2H), 7.47 (s, 1H, -*H*C=C-), 7.41-7.35 (m, 3H), 5.59 (s, 1H, Ph-C*H*-), 5.52 (d, *J* = 8.9 Hz, 1H, H-1), 4.41-4.30 (m, 2H, H-6_a, H-2), 4.06-3.99 (m, 1H, H-3), 3.84-3.69 (m, 3H, H-6_b, H-4, H-5), 2.73 (t, *J* = 7.7 Hz, 2H), 1.75-1.64 (m, 2H), 1.43-1.19 (m, 22H), 0.89 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 129.4, 128.4, 126.3, 120.5 (-H*C*=C-), 102.2 (Ph-*C*H-), 87.9 (C-1), 80.1 (C-4), 73.8 (C-3), 73.4 (C-2), 69.4 (C-5), 68.4

(C-6), 31.9, 29.69, 29.67, 29.65, 29.6, 29.4, 29.34, 29.30, 29.2, 25.6, 22.7, 14.0; LC-MS (ESI+) calcd for $C_{29}H_{46}N_3O_5$ $[M + H]^+$ 516.3 found 516.3.

Synthesis of compound 14:

Phenylacetylene (0.044 mL, 0.410 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (103 mg, 76%) as the desired product (R_f = 0.24 in 5% MeOH/DCM); mp 242-244 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.86 (s, 1H, -*H*C=C-), 7.93-7.86 (m, 2H), 7.52-7.33 (m, 8H), 5.81 (d, *J* = 9.2 Hz, 1H, H-1), 5.72 (d, *J* = 6.1 Hz, 1H, 2-O*H*), 5.68-5.64 (m, 2H, Ph-C*H*-, 3-O*H*), 4.28-4.22 (m, 1H, H-6_a), 4.03-3.95 (m, 1H, H-2), 3.87-3.79 (m, 1H, H-5), 3.78-3.69 (m, 2H, H-6_b, H-3), 3.61 (t, *J* = 9.3 Hz, 1H, H-4); ^{13}C NMR (100 MHz, d_6-DMSO) δ 146.4 (-HC=*C*-), 137.6, 130.5, 128.9, 128.0, 126.3, 125.2, 120.5 (-H*C*=C-), 100.7 (Ph-*C*H-), 87.7 (C-1), 80.2 (C-4), 73.1 (C-3), 72.8 (C-2), 68.5 (C-5), 67.5 (C-6). LC-MS (ESI+) calcd for $C_{21}H_{22}N_3O_5$ $[M + H]^+$ 396.1 found 396.1.

Synthesis of compound 15:

5-Phenyl-1-pentyne (0.062 mL, 0.410 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (113 mg, 76%) as the desired product (R_f = 0.36 in 5% MeOH/DCM); mp 230-232 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.11 (s, 1H), 7.51-7.44 (m, 2H), 7.43-7.36 (m, 3H), 7.33-7.26 (m, 2H), 7.26-7.16 (m, 3H), 5.70 (d, *J* = 9.2 Hz, 1H, H-1), 5.65-5.58 (m, 3H, Ph-C*H*-, 2-O*H*, 3-O*H*), 4.24-4.18 (m, 1H, H-6_a), 3.97-3.88 (m, 1H, H-2), 3.80-3.65 (m, 3H, H-5, H-6_b, H-3), 3.58 (t, *J* = 9.2 Hz, 1H, H-4), 2.64 (t, *J* = 7.6 Hz, 4H), 1.96-1.86 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 146.6 (-HC=*C*-), 141.7, 137.6, 128.8, 128.3, 128.2, 128.0, 126.3, 125.7, 121.0 (-H*C*=C-), 100.7 (Ph-*C*H-), 87.4

(C-1), 80.1 (C-4), 73.2 (C-3), 72.7 (C-2), 68.4 (C-5), 67.5 (C-6), 34.5, 30.5, 24.5; LC-MS (ESI+) calcd for $C_{24}H_{28}N_3O_5$ $[M + H]^+$ 438.2 found 438.2.

Synthesis of compound 16:

3-Dimethylamino-1-propyne (0.044 mL, 0.410 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford off-white solid (110 mg, 86%) as the desired product (R_f = 0.3 in 20% MeOH/DCM); mp 204-206 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.19 (s, 1H, -*H*C=C-), 7.55-7.33 (m, 5H), 5.73 (d, *J* = 9.0 Hz, 1H, H-1), 5.68-5.57 (m, 3H, Ph-C*H*-, 2-O*H*, 3-O*H*), 4.28-4.16 (m, 1H, H-6_a), 4.00-3.89 (m, 1H, H-2), 3.77-3.62 (m, 3H, H-5, H-6_b, H-3), 3.63-3.48 (m, 3H, H-4, -CH_2-N), 2.17 (s, 6H, -N(CH_3)$_2$); ^{13}C NMR (100 MHz, d_6-DMSO) δ 143.6 (-HC=*C*-), 137.6, 128.8, 128.0, 126.3, 122.9 (-H*C*=C-), 100.7 (Ph-*C*H-), 87.5 (C-1), 80.1 (C-4), 73.2 (C-3), 72.7 (C-2), 68.5 (C-5), 67.5 (C-6), 53.4 (-*C*H_2-N), 44.5 (-N(*C*H_3)$_2$); LC-MS (ESI+) calcd for $C_{18}H_{25}N_4O_5$ $[M + H]^+$ 377.2 found 377.2.

Synthesis of compound 17:

Propargyl alcohol (0.024 mL, 0.410 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (110 mg, 86%) as the desired product (R_f = 0.25 in 5% MeOH/DCM); mp 219-221 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.19 (s, 1H, -*H*C=C-), 7.50-7.45 (m, 2H), 7.42-7.37 (m, 3H), 5.73 (d, *J* = 9.3 Hz, 1H, H-1), 5.66-5.63 (m, 2H, Ph-C*H*-, 2-O*H*), 5.60 (d, *J* = 5.1 Hz, 1H, 3-O*H*), 5.20 (t, *J* = 5.7 Hz, 1H, -CH_2-O*H*), 4.53 (d, *J* = 5.7 Hz, 2H, -CH_2-OH), 4.23-4.18 (m, 1H, H-6_a), 3.98-3.91 (m, 1H, H-2), 3.79-3.65 (m, 3H, H-5, H-6_b, H-3), 3.59 (t, *J* = 9.1 Hz, H-4); ^{13}C NMR (100 MHz, d_6-DMSO) δ 147.9 (-HC=*C*-), 137.6, 128.8, 128.0, 126.3, 121.9 (-H*C*=C-), 100.7 (Ph-*C*H-), 87.4 (C-1), 80.1

(C-4), 73.2 (C-3), 72.7 (C-2), 68.4 (C-5), 67.5 (C-6), 54.9 (-*C*H_2-OH); LC-MS (ESI+) calcd for $C_{16}H_{20}N_3O_6$ 350.1 $[M + H]^+$ found 350.1.

Synthesis of compound 18:

4-Pentyn-1-ol (0.038 mL, 0.410 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford off-white solid (103 mg, 80%) as the desired product (R_f = 0.4 in 8% MeOH/DCM); mp 164-166 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.06 (s, 1H, -*H*C=C-), 7.50-7.45 (m, 2H), 7.42-7.36 (m, 3H), 5.69 (d, *J* = 9.2 Hz, 1H, H-1), 5.66-5.57 (m, 3H, Ph-C*H*-, 2-O*H*, 3-O*H*), 4.47 (s, 1H, -CH_2-O*H*), 4.24-4.18 (m, 1H, H-6_a), 4.00-3.87 (m, 1H, H-2), 3.80-3.64 (m, 3H, H-5, H-6_b, H-3), 3.58 (t, *J* = 9.1 Hz, 1H, H-4), 3.45 (m, 2H, -C*H*$_2$-OH), 2.66 (t, *J* = 7.6 Hz, 2H), 1.80-1.71 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 146.8 (-HC=*C*-), 137.6, 128.8, 128.0, 126.3, 120.9 (-H*C*=C-), 100.7 (Ph-*C*H-), 87.4 (C-1), 80.1 (C-4), 73.2 (C-3), 72.7 (C-2), 68.4 (C-5), 67.5 (C-6), 60.0 (-*C*H_2-OH), 32.1, 21.6; LC-MS (ESI+) calcd for $C_{18}H_{24}N_3O_6$ $[M+H]^+$ 378.2 found 378.2.

Synthesis of compound 19:

1-Ethynylcyclohexanol (0.053 mL, 0.410 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (112 mg, 79%) as the desired product (R_f = 0.25 in 5% MeOH/DCM); compound decomposed at 245 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.05 (s, 1H, -*H*C=C-), 7.52-7.44 (m, 2H), 7.42-7.36 (m, 3H), 5.72 (d, *J* = 9.2 Hz, 1H, H-1), 5.65-5.61 (m, 2H, Ph-C*H*-, 2-O*H*), 5.58 (d, *J* = 5.1 Hz, 1H, 3-O*H*), 4.85 (s, 1H, -C-O*H*), 4.23-4.18 (m, 1H, H-6_a), 4.00-3.92 (m, 1H, H-2), 3.78-3.65 (m, 3H, H-5, H-6_b, H-3), 3.59 (t, *J* = 9.0 Hz, 1H), 1.93-1.81 (m, 2H), 1.78-1.61 (m, 4H), 1.58-1.49 (m, 1H), 1.48-1.38

(m, 2H), 1.35-1.21 (m, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 155.7 (-HC=*C*-), 137.6, 128.8, 128.0, 126.3, 120.2 (-H*C*=C-), 100.7 (Ph-*C*H-), 87.4 (C-1), 80.1 (C-4), 73.3 (C-3), 72.6 (C-2), 68.4 (C-5), 67.9 (-*C*-OH), 67.5 (C-6), 37.7, 37.6, 25.2, 21.6. LC-MS (ESI+) calcd for $C_{21}H_{28}N_3O_6$ $[M + H]^+$ 418.2 found 418.2.

Synthesis of sugar headgroup azide 22:

Headgroup azide **22** was synthesized following literature method with slight modifications using N-acetyl-D-glucosamine as the starting material.[66] Compound **20** (1.20 g, 3.22 mmol, 1 equiv) was dissolved in MeOH (8 mL) and NaOMe (173 mg, 3.22 mmol, 1 equiv) was added to 50 mL round bottom flask. The reaction mixture was stirred for 12 hours at rt, neutralized with Amberlite IR 120 hydrogen form (soaked with the resin for 2 hours after adjusting pH to 7), filtered, concentrated and vacuum drying overnight to give brown slurry as the product. The crude product was co-distilled with toluene (3 x 10 mL) and directly used for the next step without further purification. Toluene treated compound **21** (714 mg, 2.90 mmol, 1 equiv) was dissolved in DMF (6 mL, anhydrous) followed by adding benzaldehyde dimethyl acetal (0.83 mL, 5.51 mmol, 1.9 equiv) and PTSA monohydrate (55 mg, 0.290 mmol, 0.1 equiv) under N_2 atmosphere. Then the reaction mixture was stirred under the vacuum in a rotavap at 50 °C for 2 hrs. Then the mixture was removed from the rotavap and then heated in an oil bath at 50 °C overnight under N_2 atmosphere. $NaHCO_3$ (36 mg, 0.435 mmol, 0.15 equiv) was added and stirring was continued for 30 minutes to neutralize PTSA followed by applying gravitational filtration to remove generated salt. Then DMF in the reaction mixture was removed under reduced pressure to give the crude product, which was purified by column chromatography using 2% MeOH/DCM to 10% MeOH/DCM as the eluent to afford white solid (773 mg, 72% over two

steps) as the product (R_f = 0.3 in 5% MeOH/DCM). mp 213-215 °C. ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.53-7.46 (m, 2H), 7.38-7.31 (m, 3H), 5.62 (s, 1H), 4.65 (d, *J* = 9.1 Hz, 1H), 4.37-4.29 (m, 1H), 3.89-3.74 (m, 3H), 3.63-3.52 (m, 2H), 2.00 (s, 3H); ^{13}C NMR (400 MHz, d_4-MeOH) δ 173.9, 139.0, 130.0, 129.1, 127.5, 103.0, 90.5, 82.5, 72.4, 69.9, 69.4, 57.3, 22.9.

General procedure for the synthesis of synthesis of compounds 23-32:

To a scintillation vial, azide **22** (75 mg, 0.225 mmol, 1 equiv) and alkyne (0.269 mmol, 1.2 equiv) were dissolved in the 3 mL of solvent mixture of THF: H_2O: *t*-BuOH (1:1:1). $CuSO_4$ (7.2 mg, 0.045 mmol, 0.2 equiv) and L-ascorbic acid sodium salt (18 mg, 0.090 mmol, 0.4 equiv) were added to the reaction mixture. Reaction was stirred for 24 hours at rt. Solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography using from pure DCM to 5% MeOH/DCM to afford the desired triazole product **23-32.**

Synthesis of compound 23:

1-Hexyne (0.032 mL, 0.269 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (76 mg, 82%) as the desired product (R_f = 0.2 in 5% MeOH/DCM); mp 267-269 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.96-7.90 (m, 2H, -N*H*-, -*H*C=C-), 7.51-7.45 (m, 2H), 7.43-7.36 (m, 3H), 5.85 (d, *J* = 10.0 Hz, 1H, H-1), 5.65 (s, 1H, Ph-C*H*-), 5.58 (s, 1H, 3-O*H*), 4.27-4.17 (m, 2H, H-6_a, H-2), 3.86 (t, *J* = 9.2 Hz, 1H, H-3), 3.77-3.62 (m, 3H, H-6_b, H-5, H-4), 2.59 (t, *J* = 7.5 Hz, 2H), 1.63 (s, 3H), 1.60-1.50 (m, 2H), 1.34-1.22 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.2, 146.7 (-HC=*C*-), 137.6, 128.9, 128.0, 126.4, 120.4 (-H*C*=C-), 100.8 (Ph-*C*H-), 86.0 (C-1),

80.7 (C-4), 70.4 (C-3), 68.7 (C-5), 67.4 (C-6), 55.0 (C-2), 30.9, 24.5, 22.6, 21.4, 13.6; LC-MS (ESI+) calcd for $C_{21}H_{28}N_4O_5Na$ $[M+Na]^+$ 439.2 found 439.2.

Synthesis of compound 24:

6-Chloro-1-hexyne (0.033 mL, 0.269 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (86 mg, 85%) as the desired product (R_f = 0.4 in 5% MeOH/DCM); mp 185-187 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.97-7.90 (m, 2H, -N*H*-, -*H*C=C-), 7.50-7.45 (m, 2H), 7.41-7.36 (m, 3H), 5.85 (d, *J* = 10.0 Hz, 1H, H-1), 5.65 (s, 1H, Ph-C*H*-), 5.58 (d, *J* = 5.4 Hz, 1H, 3-O*H*), 4.28-4.17 (m, 2H, H-6_a, H-2), 3.86 (m, 1H, H-3), 3.77-3.61 (m, 5H, H-6_b, H-5, H-4, -CH_2-Cl), 2.50 (t, *J* = 7.4 Hz, 2H), 1.78-1.66 (m, 4H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 170.8, 147.3 (-HC=*C*-), 137.9, 129.7, 128.8, 127.0, 121.4 (-H*C*=C-), 101.5 (Ph-*C*H-), 86.7 (C-1), 80.9 (C-4), 71.1 (C-3), 69.3 (C-5), 67.9 (C-6), 55.7 (C-2), 45.8 (-*C*H_2-Cl), 31.7, 26.6, 24.5, 23.0; LC-MS (ESI+) calcd for $C_{21}H_{27}N_4O_5NaCl$ $[M + Na]^+$ 473.2 found 473.1.

Synthesis of compound 25:

1-Octyne (0.040 mL, 0.269 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (84 mg, 84%) as the desired product (R_f = 0.5 in 10% MeOH/DCM); mp 246-248 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.96-7.89 (m, 2H, -N*H*-, -*H*C=C-), 7.51-7.44 (m, 2H), 7.43-7.35 (m, 3H), 5.84 (d, *J* = 10.0 Hz, 1H, H-1), 5.65 (s, 1H, Ph-C*H*-), 5.58 (d, *J* = 5.4 Hz, 1H, 3-O*H*), 4.28-4.16 (m, 2H, H-6_a, H-2), 3.90-3.82 (m, 1H, H-3), 3.77-3.61 (m, 3H, H-6_b, H-5, H-4), 2.58 (t, *J* = 7.4 Hz, 2H), 1.63 (s, 3H), 1.61-1.51 (m, 2H), 1.31-1.23 (m, 6H), 0.86 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100

MHz, d_6-DMSO) δ 169.1, 146.8 (-HC=*C*-), 137.5, 128.9, 128.0, 126.3, 120.4 (-H*C*=C-), 100.8 (Ph-*C*H-), 85.9 (C-1), 80.7 (C-4), 70.4 (C-3), 68.7 (C-5), 67.4 (C-6), 55.0 (C-2), 31.0, 28.7, 28.0, 24.8, 22.6, 22.0, 13.9; LC-MS (ESI+) calcd for $C_{23}H_{32}N_4O_5Na$ $[M+Na]^+$ 467.2 found 467.3.

Synthesis of compound 26:

1-Decyne (0.050 mL, 0.269 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (87 mg, 82%) as the desired product (R_f = 0.6 in 10% MeOH/DCM); mp 243-245 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.95-7.87 (m, 2H, -N*H*-, -*H*C=C-), 7.52-7.44 (m, 2H), 7.43-7.36 (m, 3H), 5.85 (d, *J* = 10.0 Hz, 1H, H-1), 5.65 (s, 1H, Ph-C*H*-), 5.57 (d, *J* = 5.4 Hz, 1H, 3-O*H*), 4.27-4.16 (m, 2H, H-6_a, H-2), 3.90-3.82 (m, 1H, H-3), 3.77-3.58 (m, 3H, H-6_b, H-5, H-4), 2.58 (t, *J* = 7.5 Hz, 2H), 1.63 (s, 3H), 1.60-1.51 (m, 2H), 1.31-1.20 (m, 10H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.1, 146.7 (-HC=*C*-), 137.5, 128.9, 128.0, 126.3, 120.4 (-H*C*=C-), 100.7 (Ph-*C*H-), 85.9 (C-1), 80.7 (C-4), 70.4 (C-3), 68.7 (C-5), 67.4 (C-6), 55.0 (C-2), 31.2, 28.73, 28.68, 28.6, 28.3, 24.8, 22.6, 22.0, 13.9; LC-MS (ESI+) calcd for $C_{25}H_{36}N_4O_5Na$ $[M + Na]^+$ 495.3 found 495.2.

Synthesis of compound 27:

1-Dodecyne (0.058 mL, 0.269 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (96 mg, 85%) as the desired product (R_f = 0.6 in 10% MeOH/DCM); mp 241-243 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.95-7.88 (m, 2H, -N*H*-, -*H*C=C-), 7.51-7.46 (m, 2H), 7.43-7.36 (m, 3H), 5.85 (d, *J* = 10.0 Hz, 1H, H-1), 5.65 (s, 1H, Ph-C*H*-), 5.57 (d, *J* = 5.4 Hz, 1H, 3-O*H*), 4.27-4.16 (m, 2H, H-

6_a, H-2), 3.90-3.82 (m, 1H, H-3), 3.77-3.58 (m, 3H, H-6_b, H-5, H-4), 2.58 (t, *J* = 7.5 Hz, 2H), 1.63 (s, 3H), 1.61-1.52 (m, 2H), 1.25 (br s, 14H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.1, 146.7 (-HC=*C*-), 137.5, 128.9, 128.0, 126.3, 120.4 (-H*C*=C-), 100.7 (Ph-*C*H-), 85.9 (C-1), 80.7 (C-4), 70.4 (C-3), 68.7 (C-5), 67.4 (C-6), 55.0 (C-2), 31.2, 28.92, 28.91, 28.7, 28.6, 28.3, 24.8, 22.6, 22.0, 13.9; LC-MS (ESI+) calcd for $C_{27}H_{40}N_4O_5Na$ $[M + Na]^+$ 523.3 found 523.3.

Synthesis of compound 28:

1-Hexdecyne (66 mg, 0.269 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (100 mg, 80%) as the desired product (R_f = 0.6 in 10% MeOH/DCM); mp 226-228 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.95-7.89 (m, 2H, -N*H*-, -*H*C=C-), 7.51-7.45 (m, 2H), 7.43-7.36 (m, 3H), 5.85 (d, *J* = 10.0 Hz, 1H, H-1), 5.65 (s, 1H), 5.57 (d, *J* = 5.4 Hz, 1H, 3-O*H*), 4.27-4.15 (m, 2H, H-6_a, H-2), 3.90-3.80 (m, 1H, H-3), 3.76-3.60 (m, 3H, H-6_b, H-5, H-4), 2.50 (t, *J* = 7.5 Hz, 2H), 1.63 (s, 3H), 1.60-1.51 (m, 2H), 1.24 (br s, 22H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.1, 146.7 (-HC=*C*-), 137.5, 128.9, 128.0, 126.3, 120.4 (-H*C*=C-), 100.8, 85.9 (C-1), 80.7 (C-4), 70.4 (C-3), 68.7 (C-5), 67.4 (C-6), 55.0 (C-2), 31.2, 29.0, 28.94, 28.90, 28.7, 28.6, 28.3, 24.8, 22.6, 22.0, 13.9; LC-MS (ESI+) calcd for $C_{31}H_{49}N_4O_5$ $[M + H]^+$ 557.4 found 557.3.

Synthesis of compound 29:

Phenylacetylene (0.030 mL, 0.269 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (81 mg, 83%) as the desired product (R_f = 0.4 in 10% MeOH/DCM); mp 275-277 °C; ^{1}H NMR (400 MHz, d_6-

DMSO) δ 8.74 (s, 1H, -*H*C=C-), 8.03 (d, *J* = 9.1 Hz, 1H, -N*H*-), 7.88-7.83 (m, 2H), 7.85-7.42 (m, 4H), 7.41-7.32 (m, 4H), 5.94 (d, *J* = 10.0 Hz, 1H, H-1), 5.71-5.64 (m, 2H, Ph-C*H*-, 3-OH), 4.34-4.22 (m, 2H, H-6_a, H-2), 3.96-3.88 (m, 1H, H-3), 3.82-3.66 (m, 3H, H-6_b, H-5, H-4), 1.64 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 170.1, 146.7 (-HC=*C*-), 137.8, 130.5, 129.3, 128.5, 128.4, 126.7, 125.6, 120.5 (-H*C*=C-), 101.2 (Ph-*C*H-), 86.6 (C-1), 80.8 (C-4), 70.7 (C-3), 69.1 (C-5), 67.7 (C-6), 55.6 (C-2), 22.9; LC-MS (ESI+) calcd for $C_{23}H_{24}N_4O_5Na$ $[M + Na]^+$ 459.2 found 459.2.

Synthesis of compound 30:

3-Dimethylamino-1-propyne (0.030 mL, 0.269 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (73 mg, 78%) as the desired product (R_f = 0.3 in 20% MeOH/DCM); mp 223-225 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.04 (s, 1H, -*H*C=C-), 7.94 (d, *J* = 9.4 Hz, 1H, -N*H*-), 7.51-7.45 (m, 2H), 7.42-7.37 (m, 3H), 5.86 (d, *J* = 10.0 Hz, 1H, H-1), 5.66 (s, 1H, Ph-C*H*-), 5.57 (d, *J* = 5.4 Hz, 1H, 3-O*H*), 4.30-4.18 (m, 2H, H-6_a, H-2), 3.85 (m, 1H, H-3), 3.79-3.63 (m, 3H, H-6_b, H-5, H-4), 3.53-3.43 (m, 2H, -CH_2-N-), 2.12 (s, 6H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.2, 143.1 (-HC=*C*-), 137.5, 128.9, 128.0, 126.4, 122.6 (-H*C*=C-), 100.8 (Ph-*C*H-), 86.2 (C-1), 80.6 (C-4), 70.4 (C-3), 68.7 (C-5), 67.4 (C-6), 55.1 (C-2), 53.2 (-*C*H_2-N-), 44.2, 22.6; LC-MS (ESI+) calcd for $C_{20}H_{28}N_5O_5$ $[M+H]^+$ 418.2 found 418.2.

Synthesis of compound 31:

4-Pentyn-1-ol (0.026 mL, 0.269 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (75 mg, 80%) as the

desired product (R_f = 0.3 in 10% MeOH/DCM); mp 217-219 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.97-7.90 (m, 2H, -N*H*-, -*H*C=C-), 7.51-7.45 (m, 2H), 7.42-7.36 (m, 3H), 5.85 (d, *J* = 10.0 Hz, 1H, H-1), 5.65 (s, 1H, Ph-C*H*-), 5.58 (d, *J* = 5.4 Hz, 1H, 3-O*H*), 4.45 (t, *J* = 5.2 Hz, 1H, -CH_2-O*H*), 4.27-4.16 (m, 2H, H-6_a, H-2), 3.86 (m, 1H, H-3), 3.77-3.61 (m, 3H, H-6_b, H-5, H-4), 3.44-3.38 (m, 2H, -CH_2-OH), 2.63 (t, *J* = 7.6 Hz, 2H), 1.76-1.67 (m, 2H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.3, 146.7 (-HC=*C*-), 137.6, 129.0, 128.1, 126.4, 120.5 (-H*C*=C-), 100.8 (Ph-*C*H-), 86.0 (C-1), 80.7 (C-4), 70.4 (C-3), 68.7 (C-5), 67.5 (C-6), 59.9 (-*C*H_2-OH), 55.1 (C-2), 32.1, 22.7, 21.6; LC-MS (ESI+) calcd for $C_{20}H_{27}N_4O_6$ $[M+H]^+$ 419.2 found 419.2.

Synthesis of compound 32:

1-Ethynyl-1-cyclohexanol (33 mg, 0.269 mmol, 1.2 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (76 mg, 74%) as the desired product (R_f = 0.55 in 10% MeOH/DCM); mp 257-259 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.96-7.90 (m, 2H, -N*H*-, -*H*C=C-), 7.50-7.45 (m, 2H), 7.43-7.37 (m, 3H), 5.88 (d, *J* = 10.0 Hz, 1H, H-1), 5.65 (s, 1H, Ph-C*H*-), 5.56 (d, *J* = 5.5 Hz, 1H, 3-O*H*), 4.84 (s, 1H, -C-O*H*), 4.29-4.17 (m, 2H, H-6_a, H-2), 3.86 (m, 1H, H-3), 3.78-3.63 (m, 3H, H-6_b, H-5, H-4), 1.99-1.88 (m, 1H), 1.85-1.75 (m, 1H), 1.70-1.64 (m, 6H), 1.54-1.22 (m, 5H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.1, 155.2 (-HC=*C*-), 137.5, 128.9, 128.0, 126.3, 119.7 (-H*C*=C-), 100.8 (Ph-*C*H-), 85.9 (C-1), 80.7 (C-4), 70.4 (C-3), 68.7 (C-5), 67.8 (-*C*-OH), 67.4 (C-6), 54.9 (C-2), 38.0, 37.4, 25.2, 22.6, 21.6; LC-MS (ESI+) calcd for $C_{23}H_{30}N_4O_6Na$ $[M + Na]^+$ 481.2 found 481.2.

General procedure for the synthesis of triazoles 33-34:

Compound with hydroxyl groups free at 2 and 3 position (40 mg, 1 equiv) was dissolved in 2 mL of the THF in a scintillation vial. The mixture which was not completely dissolved in THF was stirred in ice for 15 minutes. Pyridine (20 equiv) was added. Then acetic anhydride (4 equiv) was also added into the mixture. After the addition of the acetic anhydride and pyridine, the reaction mixture became a clear solution. The reaction was allowed to warm to room temperature for 18 hours. TLC and NMR showed that the starting material had been consumed. The mixture became opaque again after the completion of the reaction. The solvent was removed under reduced pressure. The crude was diluted with 10 mL DCM and washed with 5 mL water. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was then purified using column chromatography with a gradient solvent system from pure DCM to 1% MeOH/DCM to afford the desired product.

Synthesis of compound 33:

White solid (39.8 mg, 81%), mp 253-254 °C; R_f = 0.6 in 3% MeOH/DCM. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.42 (m, 3H, -*H*C=C-, Ar-H), 7.41-7.35 (m, 3H, Ar-H), 5.90 (d, *J* = 8.9 Hz, 1H, H-1), 5.55 (s, 1H, Ph-C*H*-), 5.53-5.44 (m, 2H, H-3, H-2), 4.45-4.37 (m, 1H, H-6_a), 3.92-3.77 (m, 3H, H-4, H-6_b, H-5), 2.72 (t, *J* = 7.5 Hz, 2H), 2.07 (s, 3H), 1.88 (s, 3H), 1.70-1.61 (m, 2H), 1.43-1.32 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.1, 149.1 (-HC=*C*-), 136.4, 129.3, 128.3, 126.1, 118.8 (-H*C*=C-), 101.8 (Ph-*C*H-), 86.1 (C-1), 78.1 (C-4), 71.7 (C-3), 71.1 (C-2), 69.6 (C-5), 68.1 (C-6), 31.2, 25.3, 22.1, 20.7, 20.2, 13.8; LC-MS (ESI+) calcd for $C_{23}H_{30}N_3O_7$ $[M + H]^+$ 460.2 found 460.2.

Synthesis of compound 34:

White solid (39.4 mg, 85%), mp 241-243 °C. R_f = 0.5 in 3% MeOH/DCM; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.42 (m, 3H, -*H*C=C-, Ar-H), 7.40-7.34 (m, 3H, Ar-H), 5.90 (d, *J* = 8.9 Hz, 1H, H-1), 5.55 (s, 1H, Ph-C*H*-), 5.54-5.44 (m, 2H, H-3, H-2), 4.45-4.36 (m, 1H, H-6_a), 3.92-3.78 (m, 3H, H-4, H-6_b, H-5), 2.71 (t, *J* = 7.5 Hz, 2H), 2.07 (s, 3H), 1.88 (s, 3H), 1.72-1.61 (m, 2H), 1.39-1.26 (m, 6H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.1, 149.2 (-HC=*C*-), 136.4, 129.3, 128.3, 126.1, 118.8 (-H*C*=C-), 101.8 (Ph-*C*H-), 86.1 (C-1), 78.1 (C-4), 71.7 (C-3), 71.1 (C-2), 69.5 (C-5), 68.1 (C-6), 31.5, 29.1, 28.7, 25.6, 22.5, 20.7, 20.2, 14.0. LC-MS (ESI+) calcd for $C_{25}H_{33}N_3O_7$ $[M + H]^+$ 488.2 found 488.2.

Synthesis of the triazole headgroup 35:

Headgroup azide **35** was synthesized following literature method with slight modification using compound **22** as the starting material.[66] To a 50 mL of round bottomed flask, compound **22** (600 mg, 1.800 mmol, 1 equiv), and 3 mL mixture of THF:pyridine (v 2:1) were charged followed by adding acetic anhydride (0.34 mL, 3.600 mmol, 2.0 equiv) dropwise to the mixture at 0 °C (ice-water bath). The resulting mixture was stirred initially at 0 °C and then allowed it to wart to rt for overnight stirring. The reaction mixture was diluted with EtOAc (30 mL), and then washed with water (5 mL). The combined organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated to afford white solid (602 mg, 89%) as the desired product. mp 210-212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.40 (m, 2H), 7.39-7.34 (m, 3H), 5.94 (d, *J* = 9.4 Hz, 1H), 5.52 (s, 1H), 5.27 (t, *J* = 9.9 Hz, 1H, H-3), 4.55 (d, *J* = 9.3 Hz, 1H, H-1), 4.35 (dd, *J* = 10.5, 4.9 Hz, 1H, H-6_a), 4.16-4.06 (m, 1H, H-2), 3.80 (t, *J* = 10.2 Hz, 1H, H-6_b), 3.71 (t, *J* = 9.4 Hz, 1H, H-4), 3.65-3.56 (m, 1H, H-5), 2.09 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 170.4,

136.7, 129.3, 128.3, 126.0, 101.4, 89.5 (C-1), 78.3 (C-4), 71.7 (C-3), 68.6 (C-5), 68.3 (C-6), 54.0 (C-2), 23.2, 20.9.

General procedure for the synthesis of triazoles 36-38:

To a 50 mL round bottomed flask, compound **35** (75 mg, 0.200 mmol, 1 equiv), alkyne (0.260 mmol, 1.3 equiv), CH_3CN (4 mL, anhydrous), CuI (7.6 mg, 0.040 mmol, 0.2 equiv) and DIEA (0.17 mL, 1.00 mmol, 5 equiv) were added in the given order. The reaction mixture was stirred at rt for 24 hrs. Then the solvent was removed to afford the crude product, which was purified by column chromatography using eluent from pure DCM to 5% MeOH/DCM to give the desired product.

Synthesis of compound 36:

1-Hexyne (0.030 mL, 0.260 mmol, 1.3 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (75 mg, 82%) as the desired product (R_f = 0.4 in 5% MeOH/DCM). compound decomposed at 275 °C; ^{1}H NMR (d_6-DMSO, 400 MHz) δ 8.05 (d, J = 9.3 Hz, 1H, -N*H*-), 8.00 (s, 1H), 7.43-7.36 (m, 5H), 6.05 (d, J = 9.9 Hz, 1H, H-1), 5.68 (s, 1H, Ph-C*H*-), 5.39 (t, J = 9.7 Hz, 1H, H-3), 4.61-4.51 (m ,1H, H-2), 4.27 (dd, J = 9.9, 4.7 Hz, 1H, H-6_a), 3.97 (t, J = 9.4 Hz, 1H, H-4), 3.91-3.83 (m, 1H, H-5), 3.77 (t, J = 9.9 Hz, 1H, H-6_b), 2.60 (t, J = 7.5 Hz, 2H), 1.99 (s, 3H), 1.62-1.50 (m, 5H), 1.33-1.22 (m, 2H), 0.88 (t, J =7.4 Hz, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.7, 169.3, 147.0, 137.2, 129.0, 128.1, 126.1, 120.6, 100.4 (Ph-*C*H-), 85.3 (C-1), 77.6 (C-4), 71.7 (C-3), 68.4 (C-5), 67.3 (C-6), 52.7 (C-2), 30.9, 24.5, 22.3, 21.4, 20.5, 13.6. LC-MS (ESI+) cacld $C_{23}H_{30}N_4O_6Na$ $[M + Na]^+$ 481.2 found 481.2.

Synthesis of compound 37:

1-Octyne (0.036 mL, 0.260 mmol, 1.3 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (70 mg, 80%) as the desired product (R_f = 0.4 in 5% MeOH/DCM). compound decomposed at 270 °C; ^{1}H NMR (d_6-DMSO, 400 MHz) δ 8.04 (d, J = 9.3 Hz, 1H, -N*H*-), 8.00 (s, 1H), 7.42-7.37 (m, 5H), 6.05 (d, J = 9.9 Hz, 1H, H-1), 5.68 (s, 1H, Ph-C*H*-), 5.39 (t, J = 9.7 Hz, 1H, H-3), 4.63-4.52 (m, 1H, H-2), 4.27 (dd, J = 9.9, 4.7 Hz, 1H, H-6_a), 3.97 (t, J = 9.4 Hz, 1H, H-4), 3.91-3.83 (m, 1H, H-5), 3.77 (t, J = 9.9 Hz, 1H, H-6_b), 2.60 (t, J = 7.4 Hz, 2H), 2.00 (s, 3H), 1.62-1.50 (m, 5H), 1.33-1.21 (m, 6H), 0.86 (t, J =6.7 Hz, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 169.6, 169.2, 147.0, 137.2, 128.9, 128.1, 126.1, 120.6, 100.4 (Ph-*C*H-), 85.3 (C-1), 77.6 (C-4), 71.7 (C-3), 68.3 (C-5), 67.3 (C-6), 52.6 (C-2), 31.0, 28.7, 28.0, 24.8, 22.3, 21.9, 20.4, 13.9; LC-MS (ESI+) calcd for $C_{25}H_{35}N_4O_6$ $[M + H]^+$ 487.3 found 487.2.

Synthesis of compound 38:

1-Decyne (0.038 mL, 0.260 mmol, 1.3 equiv) was used as the starting material. The crude product was purified by column chromatography to afford white solid (87 mg, 85%) as the desired product (R_f = 0.4 in 5% MeOH/DCM). compound decomposed at 275 °C; ^{1}H NMR (0.4 mL $CDCl_3$ + 0.1 mL d_4-MeOH) δ 7.57 (s, 1H), 7.44-7.38 (m, 2H), 7.36-7.30 (m, 3H), 5.87 (d, J = 10.0 Hz, 1H, H-1), 5.52 (s, 1H, Ph-C*H*-), 5.37 (t, J = 9.9 Hz, 1H, H-3), 4.54 (t, J = 10.1 Hz, 1H, H-2), 4.38-4.20 (m, 1H, H-6_a), 3.87-3.73 (m, 3H, H-4, H-5, H-6b), 2.63 (t, J =7.6 Hz, 2H), 2.04 (s, 3H), 1.70 (s, 3H), 1.65-1.57 (m, 2H), 1.34-1.16 (m, 10H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C NMR (0.4 mL $CDCl_3$ + 0.1 mL d_4-MeOH) δ 171.2, 170.7, 136.4, 129.1, 128.1, 125.9, 101.5 (Ph-

*C*H-), 86.4 (C-1), 78.3 (C-4), 71.5 (C-3), 69.2 (C-5), 68.0 (C-6), 53.1 (C-2), 31.6, 29.0, 28.94, 28.89, 25.2, 22.4, 22.0, 20.3, 13.7. LC-MS (ESI+) cacld $C_{27}H_{38}N_4O_6Na$ $[M + Na]^+$ 537.3 found 537.2.

Acknowledgement

This research was supported by a grant from the National Science Foundation CHE# 1313633 and Old Dominion University.

Supporting Information: In supporting information part I, the following are provided: Copies of ^1H and ^{13}C NMR spectra for compounds **7-38**; ^1H NMR spectra at variable temperatures for compounds **25** and **37** in d_6-DMSO and for compounds **9** and **25** in d_6-DMSO and D_2O; copies of 2D NMR (HSQC and COSY) spectra of compounds **9, 16, 25, 31, 33, 36** are also provided. Additional rheological studies are included. FTIR spectra of compounds **9, 10, 11, 25, 26** and their corresponding gels. The gelation test table for compounds **10** and **25** at different ratios of water and DMSO are included. In supporting information II, the HPLC-MS traces of the synthesized compounds **8-19**, **23-38** are included. This material is available free of charge via the journal's website.

References:

(1) X. Du, J. Zhou, B. Xu, Chem. Asian J. 9 (2014) 1446-1472.

(2) X. Du, J. Zhou, J. Shi, B. Xu, Chem. Rev. 115 (2015) 13165-13307.

(3) S. Datta, S. Bhattacharya, Chem. Soc. Rev. 44 (2015) 5596-5637.

(4) J. Zhou, J. Li, X. Du, B. Xu, Biomaterials 129 (2017) 1-27.

(5) P. K. Vemula, G. John, Acc. Chem. Res. 41 (2008) 769-782.

(6) S. S. Babu, S. Prasanthkumar, A. Ajayaghosh, Angew. Chem. Int. Ed. 51 (2012) 1766-1776.

(7) B. O. Okesola, D. K. Smith, Chem. Soc. Rev. 45 (2016) 4226-4251.

(8) D. B. Amabilino, D. K. Smith, J. W. Steed, Chem. Soc. Rev. 46 (2017) 2404-2420.

(9) S. Basak, J. Nanda, A. Banerjee, J. Mater. Chem. 22 (2012) 11658-11664.

(10) A. Prathap, K. M. Sureshan, Chem. Commun. 48 (2012) 5250-5252.

(11) M. Konda, I. Maity, D. B. Rasale, A. K. Das, ChemPlusChem 79 (2014) 1482-1488.

(12) S. Mukherjee, C. Shang, X. Chen, X. Chang, K. Liu, C. Yu, Y. Fang, Chem. Commun. 50 (2014) 13940-13943.

(13) L. Yan, G. Li, Z. Ye, F. Tian, S. Zhang, Chem. Commun. 50 (2014) 14839-14842.

(14) Y. Wu, T. Zhang, Z. Xu, Q. Guo, J. Mater. Chem. A 3 (2015) 1906-1909.

(15) C. S. Kesava Raju, B. Pramanik, T. Kar, P. V. C. Rao, N. V. Choudary, R. Ravishankar, RSC Adv. 6 (2016) 53415-53420.

(16) Y. Ohsedo, Polym. Adv. Technol. 27 (2016) 704-711.

(17) S. Bhattacharya, Y. Krishnan-Ghosh, Chem. Commun. (2001) 185-186.

(18) S. R. Jadhav, P. K. Vemula, R. Kumar, S. R. Raghavan, G. John, Angew. Chem. Int. Ed. 49 (2010) 7695-7698.

(19) N. Vidhya Lakshmi, T. Madhu Babu, E. Prasad, Chem. Commun. 52 (2016) 617-620.

(20) C. Ren, J. Shen, F. Chen, H. Zeng, Angew. Chem. Int. Ed. 56 (2017) 3847-3851.

(21) A. M. Vibhute, V. Muvvala, K. M. Sureshan Angew. Chem. Int. Ed. 55 (2016) 7782-7785.

(22) A. Prathap, K. M. Sureshan, Angew. Chem. Int. Ed. 56 (2017) 9405-9409.

(23) A. Motulsky, M. Lafleur, A. C. Couffin-Hoarau, D. Hoarau, F. Boury, J. P. Benoit, J. C. Leroux, Biomaterials 26 (2005) 6242-6253.

(24) A. Vintiloiu, J. C. Leroux, J. Control. Release 125 (2008) 179-192.

(25) D. Diaz Diaz, D. Kuhbeck, R. J. Koopmans, Chem. Soc. Rev. 40 (2011) 427-448.

(26) C. Ren, F. Chen, F. Zhou, J. Shen, H. Su, H. Zeng, Langmuir 32 (2016) 13510-13516.

(27) F. Trausel, F. Versluis, C. Maity, J. M. Poolman, M. Lovrak, J. H. van Esch, R. Eelkema, Acc. Chem. Res. 49 (2016) 1440-1447.

(28) K. K. Kartha, S. S. Babu, S. Srinivasan, A. Ajayaghosh, J. Am. Chem. Soc. 134 (2012) 4834-4841.

(29) A. Prathap, M. M. Shaijumon, K. M. Sureshan, Chem. Commun. 52 (2016) 1342-1345.

(30) F. Rodriguez-Llansola, J. F. Miravet, B. Escuder, Chem. Commun. (2009) 7303-7305.

(31) K. S. Lee, J. R. Parquette, Chem. Commun. 51 (2015) 15653-15656.

(32) F. Rodriguez-Llansola, B. Escuder, J. F. Miravet, J. Am. Chem. Soc. 131 (2009) 11478-11484.

(33) B. Escuder, F. Rodriguez-Llansola, J. F. Miravet, New J. Chem. 34 (2010) 1044-1054.

(34) C. Tomasini, N. Castellucci, Chem. Soc. Rev. 42 (2013) 156-172.

(35) S. S. Babu, V. K. Praveen, A. Ajayaghosh, Chem. Rev. 114 (2014) 1973-2129.

(36) G. M. Peters, J. T. Davis, Chem. Soc. Rev. 45 (2016) 3188-3206.

(37) S. W. Liao, T. B. Yu, Z. Guan, J. Am. Chem. Soc. 131 (2009) 17638-17646.

(38) G. Godeau, C. Brun, H. Arnion, C. Staedel, P. Barthelemy, Tetrahedron Lett. 51 (2010) 1012-1015.

(39) S. Roy, A. Chakraborty, B. Chattopadhyay, A. Bhattacharya, A. K. Mukherjee, R. Ghosh, Tetrahedron 66 (2010) 8512-8521.

(40) A. Srivastava, S. Ghorai, A. Bhattacharjya, S. Bhattacharya, J. Org. Chem. 70 (2005) 6574-6582.

(41) Y. Koshi, E. Nakata, H. Yamane, I. Hamachi, J. Am. Chem. Soc. 128 (2006) 10413-10422.

(42) A. Vidyasagar, K. Handore, K. M. Sureshan, Angew. Chem. Int. Ed. 50 (2011) 8021-8024.

(43) B. P. Krishnan, K. M. Sureshan, Chem. Asian J. 13 (2018) 187-193.

(44) O. Gronwald, S. Shinkai, J. Chem. Soc. Perkin Trans. 2 (2001) 1933-1937.

(45) O. Gronwald, S. Shinkai, Chem. Eur. J. 7 (2001) 4329-4334.

(46) O. Gronwald, E. Snip, S. Shinkai, Curr. Opin. Colloid Interface Sci. 7 (2002) 148-156.

(47) K. Sakurai, Y. Jeong, K. Koumoto, A. Friggeri, O. Gronwald, S. Sakurai, S. Okamoto, K. Inoue, S. Shinkai, Langmuir 19 (2003) 8211-8217.

(48) J. H. Jung, G. John, M. Masuda, K. Yoshida, S. Shinkai, T. Shimizu, Langmuir 17 (2001) 7229-7232.

(49) N. Goyal, H. P. R. Mangunuru, B. Parikh, S. Shrestha, G. Wang, Beilstein J. Org. Chem. 10 (2014) 3111-3121.

(50) N. Goyal, S. Cheuk, G. Wang, Tetrahedron 66 (2010) 5962-5971.

(51) H. P. R. Mangunuru, J. R. Yerabolu, D. Liu, G. Wang, Tetrahedron Lett. 56 (2015) 82-85.

(52) H. P. R. Mangunuru, J. R. Yerabolu, G. Wang, Tetrahedron Lett. 56 (2015) 3361-3364.

(53) G. Wang, A. Chen, H. P. R. Mangunuru, J. R. Yerabolu, RSC Adv. 7 (2017) 40887-40895.

(54) G. Wang, S. Cheuk, K. Williams, V. Sharma, L. Dakessian, Z. Thorton, Carbohydr. Res. 341 (2006) 705-716.

(55) X. Nie, G. Wang, J. Org. Chem. 71 (2006) 4734-4741.

(56) G. Wang, S. Cheuk, H. Yang, N. Goyal, P. V. N. Reddy, B. Hopkinson, Langmuir 25 (2009) 8696-8705.

(57) G. Wang, H. Yang, S. Cheuk, S. Coleman, Beilstein J. Org. Chem. 7 (2011) 234-242.

(58) H. C. Kolb, M. G. Finn, K. B. Sharpless, Angew. Chem. Int. Ed. 40 (2001) 2004-2021.

(59) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, Angew. Chem. Int. Ed. 41 (2002) 2596-2599.

(60) Q. Wang, T. R. Chan, R. Hilgraf, V. V. Fokin, K. B. Sharpless, M. G. Finn J. Am. Chem. Soc. 125 (2003) 3192-3193.

(61) S. Chittaboina, F. Xie, Q. Wang, Tetrahedron Lett. 46 (2005) 2331-2336.

(62) L. R. Steffel, T. J. Cashman, M. H. Reutershan, B. R. Linton, J. Am. Chem. Soc. 129 (2007) 12956-12957.

(63) S. Sun, P. Wu, J. Phys. Chem. A 114 (2010) 8331-8336.

(64) M. K. Nayak, B. H. Kim, J. E. Kwon, S. Park, J. Seo, J. W. Chung, S. Y. Park, Chem. Eur. J. 16 (2010) 7437-7447.

(65) P. Y. Chong, P. A. Petillo, Org. Lett. 2 (2000) 2113-2116.

(66) Y. Tomabechi, M. A. Squire, A. Fairbanks, J. Org. Biomol. Chem. 12 (2014) 942-955.

Highlights:

- Molecular gelators were rationally designed from D-glucose and D-glucosamine
- 4,6-*O*-benzylidene acetal protected D-glucosyl triazoles were organogelators
- The 3-hydroxyl group was important for molecular assembly
- Naproxen formed co-gels with a gelator and slowly diffused to aqueous phase