Synthesis, Characterization and Application of Sugar-Based Low Molecular Weight Gelators

Ifeanyi Simeon Okafor

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SYNTHESIS, CHARACTERIZATION AND APPLICATION OF SUGAR BASED LOW MOLECULAR WEIGHT GELATORS

by

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B.Tech. December 2007, Federal University of Technology Owerri, Nigeria
M.Sc. May 2016, Old Dominion University

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Old Dominion University in Partial Fulfillment of the
Requirement for the Degree of

DOCTOR OF PHILOSOPHY

CHEMISTRY

OLD DOMINION UNIVERSITY
December 2017

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Carl Busacca (Member)
Yaohang Li (Member)
ABSTRACT

SYNTHESIS, CHARACTERIZATION AND APPLICATION OF SUGAR BASED LOW MOLECULAR WEIGHT GELATORS

Ifeanyi Simeon Okafor
Old Dominion University, 2017
Director: Dr. Guijun Wang

Low molecular weight gelators (LMWGs) are an interesting class of compound that have gained considerable attention especially because of their potential applications for soft biomaterials. Carbohydrate based low molecular weight hydrogelators and organogelators are able to self-assemble and form ordered supramolecular structures, which are useful for exploring biomedical applications. The resulting gelators are responsive to external stimuli because of the weak non-covalent intermolecular forces and interaction that influences self-assembly. Stimuli-responsive supramolecular organogels with interesting properties in response to external environmental stimuli have gained considerable attention due to their applications in biomaterials, sensors and for drug delivery.

One of the major challenges in the field of small molecule gelation is understanding the mechanism of gelation. Consequently, the use of structural templates in the design and synthesis of LMWGs cannot be over emphasized. A review of the recent progress that has been made in the design and application of LMWGs will be discussed. This dissertation will also highlight some of the work that have been done in our research group.
This dissertation also explores the investigation of the influence of different substituent in the anomeric position on carbohydrate on gelation and the influence of different functional groups such as triazole, urea and amide on gelation. Previously, we have shown that α-O-methyl-D-glucosamine derived amides and ureas are effective low molecular weight gelators. In order to understand the structural requirement for the self-assembling and the gelation properties, a series of α-O-butyl-D-glucosamine derived amides and ureas were synthesized and characterized using rheology, optical microscope and NMR studies. The synthesis and gelation property study of a series of peracetylated lactose and maltose triazole derivatives will also be discussed. Results from this study showed that the maltosyl based triazole derivatives were effective gelators while the lactosyl based triazole derivatives were poor gelators. NMR studies also showed that the configuration of the sugar moiety played a significant role towards gelation.

Furthermore, to discover smart organogelators with built-in functionality that would be responsive to external stimuli, a series of sugar based UV and pH responsive organogels were synthesized. The compounds were characterized using NMR and LCMS. The gelation ability of the compounds was characterized in various solvents including non-polar solvents, polar solvents and a mixture of solvents. The resulting gels were observed to be stable but the gel matrix was disrupted when exposed to UV light and in basic pH solutions.

Keywords: Low molecular weight gelators, supramolecular gelators, carbohydrate, UV light, pH.
This dissertation is dedicated to my family and friends for all their love and support;

Late father: *Simeon Anachebe Okafor*

Mother: *Adline Anene Okafor*
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<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DDS</td>
<td>drug delivery systems</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMATr</td>
<td>3-dimethylaminotrityl group</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>EDC</td>
<td>1-ethyl-3-(3-dimethylaminopropyl) carbodiimide</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>Et$_3$N</td>
<td>triethylamine</td>
</tr>
<tr>
<td>FESEM</td>
<td>Field emission scanning electron microscope</td>
</tr>
<tr>
<td>H$_2$O</td>
<td>water</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectrometry</td>
</tr>
<tr>
<td>IPA</td>
<td>isopropanol</td>
</tr>
<tr>
<td>LCMS</td>
<td>Liquid chromatography mass spectrometry</td>
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<td>LMHG$s$</td>
<td>low molecular weight hydrogelators</td>
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<tr>
<td>LMOG$s$</td>
<td>low molecular weight organogelators</td>
</tr>
<tr>
<td>MP</td>
<td>melting point</td>
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<tr>
<td>MTT</td>
<td>3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide</td>
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<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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<tr>
<td>PAA</td>
<td>polyacrylic acid</td>
</tr>
<tr>
<td>PAN</td>
<td>polyacrylonitrile</td>
</tr>
<tr>
<td>PPG</td>
<td>photolabile protecting group</td>
</tr>
<tr>
<td>PSOG</td>
<td>phase selective organogelation</td>
</tr>
<tr>
<td>PTSA</td>
<td>p-Toluenesulfonic acid</td>
</tr>
<tr>
<td>PVA</td>
<td>polyvinyl alcohol</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning electron microscope</td>
</tr>
<tr>
<td>TEM</td>
<td>Transmission electron microscope</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>UV-Vis</td>
<td>ultraviolet and visible</td>
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CHAPTER 1

INTRODUCTION TO LOW MOLECULAR WEIGHT GELETORS (LMWGs)

1.1 INTRODUCTION

Supramolecular gels are semi-solids that are able to immobilize an organic or aqueous solvent to form supramolecular or physical gel. The factors that influence the formation of the supramolecular gels is as a result of non-covalent intermolecular forces such as hydrogen bonding, $\pi-\pi$ interactions, hydrophobic forces and van der Waals interactions which results in the formation of one dimensional structures such as fibres. The interaction of the individual fibres leads to the formation of a gel.$^{1-4}$ The weak non-covalent interactions that promote gelation result in the formation of reversible yet stable physical gels. These physical gels are also called supramolecular gels. Interestingly, the composition of a gel is made up of more than 90% liquid, yet resulting in the formation of a semi-solid like substance.$^{5,6}$ Research in the area of molecular gelators has increased tremendously as shown in Figure 1. Less than 100 citations were recorded in 1989 while the number of cited publications on molecular gelation has increased tremendously to more than 4000 in 2013.$^{7}$ Furthermore, gels have gained extensive attention for applications in the fields of biology, materials, environment, and biomedicine science. Other applications of gels are in food processing, catalysis, sensors, tissue engineering.$^{8-14}$ There have been other interesting definition of gels especially the one by P. J. Flory, which states that a gel can defined as “a colloidal dispersion with a continuous structure over macroscopic dimensions, which is permanent on the analytical time scale, and which is solid-like in its rheological behavior”.$^{15}$ A simple qualitative analysis for gelation is the inversion analysis. Typically, a small amount of the gelator molecule is dissolve in a particular solvent or solvent mixture in a vial by heating. The solution is then allowed
cool to room temperature (rt) and left undisturbed for about an hour, allowing the gelation process to occur. The vial in which the gel is formed is then inverted and if no liquid is observed to be flowing, a gel is said to have been formed.

![Figure 1](image.png)

**Figure 1.** Histogram of citations by year to “molecular gels” in the Web of Science. Reproduced with permission from ref. 7.

The gel formed can be characterized using various analysis instruments including optical micrograph, scanning electron microscope (SEM) and transmission electron microscope (TEM) to determine the morphology of the gel.\textsuperscript{16} The viscosity and elasticity of the gel is determined using rheometer. Rheometer is an instrument used to determine how solid or liquid the gel is, based on its response to mechanical stress or strain. The instrument compares the storage modulus of the gel to its loss modulus. For elastic gels, the storage modulus is always greater than the loss
modulus.\textsuperscript{17} Gels can also be classified as either polymer gels (chemical gels) or supramolecular gels (physical gels).

\section*{1.2 LOW MOLECULAR WEIGHT GELETORS (LMWGs)}

Low molecular weight gels also referred to as physical gels or supramolecular gels are a class of gel that is formed by non-covalent interactions. Low molecular weight gelators are classified into low molecular weight organogelators (LMOGs) if the solvent is an organic solvent or a mixture of an organic solvent and an aqueous solvent and low molecular weight hydrogelators (LMHGs) if water is the solvent. The proposed mechanism of gelation in physical gels relies on the aggregation of the gelators by non-covalent interactions such as hydrogen bonding to form a one-dimensional structure in the nanoscale. The one dimensional fibres formed then undergoes further self-assembling (interact with one another) to form either micelles, vesicles, ribbons, tubules in the microscale etc.\textsuperscript{1,3,4,7} These higher order microfibers become entangled, and effectively trap solvent within their gel matrix. In low molecular weight gelator, the solvent molecules simply become trapped in the gel matrix via capillary forces but do not help to comprise the gel matrix. The distinctive advantage of LMWGs over polymer-based gelators is that low molecular weight gelators are thermo-reversible because of the non-covalent forces in the gel matrix. It is important to note that some polymer gels are thermally reversible, while some simply exhibit volumetric changes at various temperature.\textsuperscript{1,18}

Chapter 2 of this dissertation will discuss the synthesis and gelation property study of a series of peracetylated lactose and maltose triazole derivatives. The motivation for this study was influenced by the previous work done by Wang group.\textsuperscript{19} The previous study which involved the
monosaccharide (D-glucose) triazole derivatives were observed to be effective gelators. The glycosyl triazoles synthesized included long and short chain carboxylic acid derivatives, long and short terminal alcohol derivatives, cyclic alcohol derivatives, phenyl derivatives, alkane derivatives and dimer compounds. The gelation properties of these derivatives were analyzed. Gel test results showed that the short chain carboxylic acid derivative was a poor gelator while the long chain carboxylic acid derivative was able to form gel in a mixture of DMSO and water. A similar trend was observed for the alcohol derivatives as the short chain alcohol derivatives were poor gelators while the long chain and cyclic alcohol derivatives were better gelators in various solvents tested including DMSO and water mixture and ethanol and water solvent mixtures. The phenyl derivatives, alkene and dimeric derivatives also formed gel in at least one of the solvents tested. The stability and elasticity of some gels were also studies using rheology. For all the gels analyzed, their storage modulus was greater than the loss modulus, which showed that the gels were elastic. The morphology of the gels was also studies using optical micrographs. The gels were observed to form different morphology ranging from formation of uniform fibrous network to entangled fibrous network. The study however did not study the gelation properties of disaccharides triazole derivatives.

The synthesis and systematic characterization of a series of photo-responsive sugar-based gelators will also be presented here. The synthesis and characterization of carbohydrate-based LMWGs that are responsive to external stimuli is a growing area in supramolecular chemistry because of their numerous applications as functional smart materials. There has been a rapid interest in the area of responsive supramolecular materials with intrinsic flexible physical and chemical properties. Examples of external stimuli that supramolecules are responsive to include
pH,\textsuperscript{22} temperature,\textsuperscript{23} enzymes\textsuperscript{24} and light.\textsuperscript{25} Light activated material is of particular interest as it can be remotely applied for a short amount of time. Other advantages of light responsive supramolecules include the ease of control and its high spatial and temporal precision.\textsuperscript{26} The design of carbohydrate based gels that are responsive to UV light irradiation is of interest to us as they have potential application as drug delivery because of their compatibility and eco-friendly properties. This work test the hypothesis that in the presence of UV light, the gelator molecule would be cleaved and hence would have potential application for biological studies.

The synthesis and characterization of a series of $\alpha$-O-butyl-D-glucosamine derived amides and ureas will be discussed in Chapter 4. A number of studies have shown that functional groups including urea, amide and triazole, influences gelation. In 2009, Wang group reported the synthesis of amide derivatives of 4,6-$O$-benzylidene methyl-$\alpha$-D-glucopyranoside.\textsuperscript{27} The report showed that the amide functional group played a role in gelation. The report however, did not study the influence of the anomeric position on gelation. Chapter 4 test the hypothesis that urea based gelators perform better than amide based gelators because of the extra hydrogen bonding in the urea functional group. The effect of hydrogen bonding to gelation was analyzed using $^1$H NMR at varying temperatures and varying concentration of the gelators.

The goal of the work presented here is thus to synthesize novel responsive sugar based gelators that are responsive to external stimuli such as pH and UV light. The potential application of these gelators for controlled release of trapped drugs will also be presented.
The compounds synthesized were purified using column chromatography using a solvent mixture of DCM:hexane:MeOH and were characterized by TLC, LCMS and NMR. In chapter 2, the synthesis of disaccharides triazole derivatives was discussed and the effect of disaccharide on gelation of sugar based triazoles was addressed. This work also aims at giving us more understanding on the effect of different substituents that influence gelation. Chapter 4 discussed the effect of the anomeric position on gelation by changing the anomeric substituent from methyl to butyl group. The properties of the gels obtained including their stability and optical images were obtained using rheometer and optical microscopy. The effect of UV light on the gelators was also characterized by NMR and TLC and LCMS.

1.3 BACKGROUND

Over the past few decades, research involving the use of LMWGs has gained great attention especially because of their application including drug delivery where a curcumin drug was encapsulated into a gel matrix and the drug was released after the gelator was cleaved using an enzyme, self-healing hydrogels where a gel has the property to self-heal especially after a hole was punched in the middle of the gel and protein separation using supramolecular electrophoresis. Understanding the structural requirement for molecules to form gel has been a challenging concept in this field. Most gelator molecules are discovered by serendipity. Interestingly, extensive research in the area of molecular gelators has shown that some general structural features can effect gelation. Studies have shown that hydrogen bonding plays a major role in gelation. For example, compounds that contain the various functional groups including alcohols, ureas, esters, carboxylic acids and amides have proven to be useful for gelation.
Others are triazole and carbamates.\textsuperscript{19,35} Moreover, compounds of biological origin and natural products such as amino acids, peptides, peptoids, carbohydrates, nucleic acids, cholesterol have been reported to be effective gelators.\textsuperscript{31,36-39}

In contrast to LMWGs, polymer gels are also called chemical gels because of the strong covalent interaction that exit in the gels. Polymer gels are typically stronger gels. There have been many reports on the synthesis and characterization of polymer.\textsuperscript{40-42} Polymer gels have found wide applications in the chemical or commercial industry such as the cosmetics, food and pharmaceutical industry especially because of their strength. The mechanism of gelation in polymer gels depends on creating a crosslinked network that is able to entrap the solvent. The gels formed are typically strong with a high degree of elasticity because of the covalent bonds in the cross-linked network. Common examples include polyvinyl alcohol (PVA, used in the plastic and paper industry), polyacrylic acid (PAA, used in cosmetics and paint industry as thickening agents), polyacrylonitrile (PAN, used in the fiber industry) and polyacrylamides (used in contact lenses). Polymer gels are also responsive to external stimuli. They undergo deformation under the influence of external stimuli such as pH and temperature cause the polymer gel to shrink or swell reversibly.

1.3.1 MECHANISM OF GELATION IN LOW MOLECULAR WEIGHT GELATORS

Solvent plays a fundamental role during gelation. The properties of the solvent such as polarity, viscosity, functional group and hydrophobic-hydrophilic activities play a sacrosanct role in determining gelation.\textsuperscript{43,44} The properties of the solvents determine if there exit a balance of gelator-solvent interaction which also plays a role in gelation. Moreover, the balance of gelator-gelator
interaction is also determined by the solvent property. Solvent also helps in nucleation and growth processes of the self-assembly which eventually promotes gelation.\textsuperscript{45,46} The chemical properties of the gelator molecule is also vital in determining if a molecule would be a good gelator. In order to have an insight into the mechanism of gelation, a gel can be classified into 3 groups; primary, secondary and tertiary gels.\textsuperscript{3} Aggregation of the gelators at the molecular level determines the primary structure of the gel. The primary structure has a scale of angstrom to nanometer. The secondary structure is determined by the morphology of the aggregation including micelles, fibers, ribbons, vesicles and sheets. The secondary structure is also determined by the molecular structure of the gelator. It is on a nanometer to micrometer scale.\textsuperscript{47} Finally, the tertiary structure of a gel which is in a micrometer scale to a millimeter scale is formed by the interaction of the individual aggregates.\textsuperscript{3}

### 1.3.2 CARBOHYDRATE BASED GELATORS

Generally, sugar is a source of energy to organism and glucose plays a role in the metabolism of organisms. Deoxyribose and ribose in DNA and RNA respectively, starch present in plants, cellulose present in the walls of plants and glycogen present in animals are other forms of sugar in nature. Carbohydrate based LMWGs have gained splendid interest over the last few decades especially because of its abundance, availability and its biodegradable properties. Interest in carbohydrate based LMWGs have also increased because LMWGs are non-toxic, eco-friendly and biocompatible (Figure 2).\textsuperscript{48} The structural diversity of carbohydrate also makes them an ideal building block for gelation. The various hydroxyl groups are responsible for hydrogen bonding which plays a role in gelation. The hydroxyl groups can also be functionalized to introduce functional groups such as urea, carbamates and amide to the compound. Carbohydrates are also
important for biological applications as carbohydrate-protein interactions are vital in viral infection, blood coagulation, immune response, inflammation and embryogenesis.\textsuperscript{49,50} Due to these advantages, research in the facet of sugar based gelators have also received great attention as shown in \textbf{Figure 3}.\textsuperscript{48}

\textbf{Figure 2.} Advantages of carbohydrate-based low molecular weight gelators. Reproduced with permission from ref. 48.

\textbf{Figure 3.} Research progress in the application of carbohydrate based gelators. Reproduced with permission from ref. 48.
1.3.2.1 CARBOHYDRATE BASED METHYL 4,6-O-BENZYLIDENE DERIVATIVES

Methyl 4,6-\(O\)-benzylidene derivatives of carbohydrates are monosaccharides that are protected at 4 and 6 positions by the treatment of carbohydrates with benzaldehyde and zinc (11) chloride.\(^5\) These monosaccharides could be glucose, galactose and mannose and examples of such molecules are shown in Figure 4. The gelation properties of these derivatives were studied to understand their structural requirements for gelation. As shown in Figure 4, the structural characteristics of these derivatives include protection of the 1-OH group by a methyl group, protection of the 4-OH and 6-OH groups with benzaldehyde dimethyl acetal groups and finally, the presence of free 2-OH and 3-OH groups. In 1998, Shinkai and co-workers investigated the influence of protecting the 4 and 6-OH groups on gelation, compounds 1-3 in various solvents such as non-polar solvents, polar solvents, aromatic solvents, aliphatic solvents and aqueous solvents. The difference in the structure of the compounds is the absolute configuration of the C-2 and C-4.\(^5\)\(^1\)\(^5\)\(^2\)

![Chemical structures of methyl, 4-OH, 6-OH protected carbohydrate.](image)

**Figure 4.** Chemical structures of methyl, 4-OH, 6-OH protected carbohydrate.
From the gel studies, it was inferred that all the 3 compounds were excellent gelators in most of the solvents tested as they were able to form a stable gel in at least 6 of the solvent tested at a concentration of 1.0 wt%. In 1999, the gelation properties of the β-derivatives of the 4,6-OH protection, compounds 4-6 were also investigated by Shinkai group in a bid to understand the influence of the aromatic position on gelation. It was concluded that changing the stereochemistry of the anomeric position influences the gelation properties of the compounds. While the β-derivatives of compound 4 and 6 also behaved as good gelators similarly to their α-derivatives counterparts in the various solvent tested, the β-derivative of compound 5 was observed to be an ineffective gelator in the solvent tested. In other to understand the structural requirement for gelation, X-ray diffraction analysis was performed on the crystals of compound 1. X-ray crystal structure showed the interaction of the molecules of compound 1 due to the two different hydrogen bonding sites from the 2-OH and 3-OH groups.

Wang’s group has studied the gelation abilities of diverse methyl 4,6-O-benzylidene-α-glucopyranose derived LMWGs by functionalizing the 2-OH and 3-OH to form carbamates, amide, urea and ester with the general structures 7-13, where the R group range from aromatic group, long chain aliphatic group, short chain aliphatic group, cyclo-alkane group, terminal alkyne, halo-alkane group to alkene group, Figure 5. The influence of the different functional groups as well as the different R groups on the self-assembly process were studied.27,31,53-55
Figure 5. Molecular structure of methyl 4,6-O-benzylidene-α-methyl derivatives of different sugar compounds, 7-13.

To understand the influence of carbamate on gelation, a series of N-linked, 7 and O-linked carbamates, 8 were synthesized as shown in Figure 6 and tested for their gelation abilities in various solvents. Compounds 7a-7c are good gelators in aqueous solvents. Both ethyl derivative 7a and isobutyl derivative 7c were able to form gels in pure water at concentrations lower than 1.0 wt %. The n-butyl derivative 7b, however does not form gels in water. For the O-linked carbamates, none of the compounds tested formed gel in water and hexane. However all the compounds tested formed gel in at least one of the solvents tested.
Furthermore, a series of urea and amide derivatives were synthesized as shown in Figure 7. Their gelation properties were also analyzed. For the amide derivatives, the aliphatic derivative, compound 9a formed gel in aqueous solution and hexane while the aromatic derivative, 9b also formed gel in at least one of the solvent tested. The urea derivatives also showed good gelation abilities as the analogs tested formed gel in at least one of the solvent. Urea which is an important nitrogen-containing metabolites in the human body is a by-product of protein metabolism that is formed in the liver. The toxicity of urea meant that it must be filtered from the blood and excreted in the urine.
The ester derivatives of the monosaccharide carbohydrate were also synthesized. Their structures are shown in Figure 8. The ester derivatives of the general structure 11 and 13 formed stable gels in water and hexane while the ester derivatives of the general structure 12 did not form a hydrogel.
1.3.2.2 CARBOHYDRATE BASED AMPHIPHILIC DERIVATIVES

Amphiphilic that are made up of a carbohydrate polar headgroup that is connected to a non-polar aliphatic alkyl group via amide, triazole and ester functional groups have been reported to form fibers or ribbon in water via non covalent interactions including hydrogen bonding and van der Waals forces.\(^5^7\) Lipids share similar properties with carbohydrate-based amphiphilic because of the non-polar hydrocarbon groups and the polar hydrophilic carbohydrate groups.

In 2012, Nandi and co–workers reported the synthesis of a series of low molecular weight amphililes gelators based on D-glucose (Figure 9). The influence of varying the hydrocarbon chain length from C\(_{11}\) to C\(_{15}\) on gelation was investigated.\(^5^8\) The amphiphilic were synthesized by converting hydroxycarboxylic acids such as malic acid (in the case of compound 14 analogs) and tartaric acid (for compound 15 analogs) in one step into the corresponding \(O\)-acylated anhydrides by reaction with the corresponding fatty acid chlorides. A ring opening of the intermediate \(O\)-acylated anhydrides formed was carried out by reacting with the primary alcohol of the D-glucose sugar to afford compounds 14 and 15 derivatives. Gelation studies show that the analogs are effective gelators in organic solvents and water. While compound 15 analogs were able to form stable hydrogels, compound 14 derivatives did not form a stable hydrogel. Also, compound 15a was a better gelator among the compound tested as it is a good gelators in most of the solvents tested including water while the other derivatives were only able to for gel in only few of the solvents tested. This variation in gelation properties is testament to the influence of H-bonding and van der Waals force of attraction in gelation. The studies also show that the long chain derivative, compound 14c formed a very stable hydrogel at rt with a minimum gelator concentration of 3.1%. 

w/v while the shorter chain length, 14b formed a stable hydrogel only at a lower temperature (T_{gel} = 20 °C).

Figure 9. Structures of synthesized carbohydrate based amphiphilic derivatives.

Oriol’s group reported the synthesis and characterization of glycoamphilile hydrogels. In this report, the polar carbohydrate head group was connected to the non-polar alkyl chain via triazole as shown in Figure 10. The studies investigated the effect of varying disaccharide polar head group on gelation. The gelation properties of the amphiphilic glycolipids were tested in different solvents including polar and non-polar organic solvents and water. The lactose derivative, 16 formed a stable hydrogel at a concentration of 1.0 wt % while the cellobiose derivative, 17 also formed a stable hydrogel at a concentration of 0.5 wt %.

Figure 10. Structures of synthesized glycolipids.
In a related report from the same group, the gelation properties of maltose-based amphiphiles were discussed. The influence of triazole on gelation was studied by comparing the gelation abilities of a series of amphiphiles connected via a triazole ring with another series of amphiphiles connected via an amide as shown in Figure 11. It was observed that only the compounds that contain a triazole ring 20 and 21 formed a hydrogel at 1.0 wt %, similarly to what was observed for compounds 16 and 17. The gelation abilities of compounds 16, 17, 20 and 21 can be attributed to the π-π stacking interactions of the triazole ring as NMR studies proved that triazole functional group and hydrogen bonding were a critical factor to promoting gelation as the proton peak of the triazole ring experienced an upfield shift when water is added to a DMSO solution.

Figure 11. Structures of a series of maltose based amphiphiles.
1.3.2.3 CARBOHYDRATE BASED DENDRITIC DERIVATIVES

Dendrimers can be defined as highly branched macromolecules with interesting shapes and diverse functionality.\textsuperscript{61} Interest in the synthesis of dendrimers has greatly increased in recent years after Fritz Vogtle first discovered dendrimers in 1978. There have been numerous reports of the self-assembly of dendritic gelators based on poly(amide), poly(ether) and poly(amino) functionality.\textsuperscript{62} There is however, insufficient literature reports on the synthesis and characterization of sugar-based dendrons.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structures.png}
\caption{Structures of novel glucose based dendrons.}
\end{figure}

In 2013, Prasad group developed a novel poly (aryl ether) dendron containing a sugar moiety. The gelation properties of these dendrons were investigated (Figure 12).\textsuperscript{63} The two compounds formed gel in various systems. While compound 22 formed a stable organogel in a mixture of DMSO-H\textsubscript{2}O systems (1:9) at a minimum gelation concentration of 0.1\% (w/v), compound 23 formed a
stable organogel in alcoholic solvents. The gelation ability of these compounds was influenced by hydrogen bonding and π-π interaction. The morphological properties of the gels formed were characterized by TEM and SEM. TEM measurements on the xerogel obtained from compound 22 shows that the gel formed a 3D entangled fiber aggregate structure with a diameter of range of 100-150 nm and a length of several micrometers. Compound 23 also exhibited fibrillary structure as determined by TEM.

In another report, Pati and co-workers synthesized a series of glycopeptide dendron conjugates, compounds 24-27 (Figure 13). The gelation properties of the compounds were characterized. Studies showed that the unprotected sugar compounds, compounds 25 and 27 formed gels in DMSO while compound 24 formed gel in acetonitrile at a minimum gelation concentration of 0.7 wt%. The increased hydrophilicity of compound 26 disrupts the gelation network of the compound.

**Figure 13.** Structures of compounds 24-27.
1.3.3 AMINO ACID BASED GELATORS

There has been a growing interest in the development of new LMWGs of different origin despite the numerous libraries of low molecular weight gelators. Amino acid derivatives represent another class of compound that have the ability to form gel in polar and non-polar organic solvents. There have been many reports on this class of gelators.\textsuperscript{65-68} Interestingly, there is insufficient report on the synthesis and study of gelation properties of novel gelators from glycosylated amino acid. Recent report shows that a glycosylated-amino acid scaffold with inherent molecular chirality and numerous hydrogen bonding sites has the potential to be effective gelators with improved structural diversity and functionality.\textsuperscript{69} Xu’s group in 2007 reported the gelation properties of two peptide-sugar conjugates as shown in \textbf{Figure 14}.\textsuperscript{70}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structures.png}
\caption{The chemical structures of Nap-L-Phe-Dglucosamine (28) and Nap-D-Phe-D-glucosamine (29).}
\end{figure}

Both compounds formed an effective hydrogel at a concentration of 0.2 wt %. Obtaining a balance between hydrophobicity and hydrophilicity was critical for gelation. Furthermore, the morphological properties of the gels were determined using TEM. TEM of the hydrogels from compound 28 showed the formation of helical fiber with a width range of 27-55 nm while the hydrogel from compound 29 formed fibers with a width range of 35-50 nm. Biocompatibility
analysis of the gels showed that compound 29 was more biocompatible. With this result, the self-healing ability of compound 29 was studied. The study showed that compound 29 possess self-healing properties on wounds on the skin of mice.

The Xu group in 2012 also reported the synthesis of a series of novel hydrogel containing a nucleobase, an amino acid and a glycoside (Figure 15). The gelation ability of the compounds were tested in various solvents. Gel result showed that all the compounds formed hydrogel at a concentration of 3.0 wt%. Studies also showed that the gels formed were also biocompatible.

![Figure 15](image-url) The molecular structures of the hydrogelators 30-33 based on the conjugates of nucleobase, amino acid.
Most recently, Li and co-workers reported the synthesis and characterization of a supramolecular gel containing a glycosylated amino acid unit as shown in Figure 16. The gelation ability of compound 34 was tested in various solvents. The compound formed an effective translucent gel in DCM, chloroform, chlorobenzene, m-dichlorobenzene and o-dichlorobenzene at rt. An opaque organogel was formed in alcoholic solvents at lower temperature except in isobutanol. The compound however did not form gel in water, hexane, methanol, ether, ethyl acetate, xylene and DMF. The morphology of the gels formed differs in different solvent. TEM images of the gels ranges from thicker fiber formation with diameters of 20 -22 nm in DCM and chloroform to the formation of well-defined nanofibrous structures of 18 nm in width in the alcoholic solvents, chlorobenzene, m-dichlorobenzene, o-dichlorobenzene, and aqueous solvents. Rheological studies also show that the elasticity of the gel also vary with different solvent. The gels formed by chloroform and ethanol has high mechanical strengths and this may be due to the formation of compact microstructure networks from TEM and SEM analysis.

Figure 16. Structure of Fmoc-Asp (Glu)-OtBu.

In 2014, Lin and co-workers reported a modest example of the formation of a supramolecular hydrogels as a potential biomaterial via the intramolecular binding of a phenyl-perfluorophenyl pair in the structure of the hydrogelator. The peptides, 35 and 36 were synthesized by solid phase peptide synthesis, Figure 17. The gelation properties of these compounds were tested. Compound
was reported to form a hydrogel at a concentration of 1 wt% in pH 5.0 while compound 36 formed a clear solution at a concentration of 1-3 wt%. The formation of hydrogel by compound 35 may be directly due to the pentafluorobenzyl group that is connected to the N-terminus of the L-phenylalanine.

In another report, Liu and co-workers reported the synthesis and gelation studies of a series of L-glutamate-based dendrons containing Figure 18. The compounds were able to form gel in hexane and water. The driving force of gelation of the glutamate dendrons can be attributed to the hydrogen bonds between the amide groups and the π-π stacking between the aromatic rings.

![Figure 17. Chemical structures of compounds 35 and 36.](attachment:image1.png)

![Figure 18. Molecular structures of glutamate-based dendrons gelators](attachment:image2.png)
1.4 STIMULI RESPONSIVE GELATORS

Low molecular weight gelators that are responsive to external stimuli offer promising opportunities for designing and constructing interesting novel functional materials. These LMWGs can respond to external stimuli such as temperature, light, pH, and enzymes. Effect of the external stimuli to the gel range from color change to gel-to-sol transitions. Others effects of external stimuli on gels are isomerization, dimer formation, change in morphology and gel-to-gel transitions.

1.4.1 pH RESPONSIVE GELATORS

pH responsive gelators consist of an acid or a base-degradable groups that either accept or release a proton in response to changes in pH of the environment. The study of pH responsive gelators have gained tremendous importance especially because of their ability of mimic various biological phenomena. These pH responsive gelators induces a gel to sol transition over a period of time upon pH change. Wang’s group reported a series of interesting acid labile carbohydrate-based supramolecular organogelator Figure 19.

![Figure 19. Structure of pH responsive gelator.](image-url)
The gelation properties of the compounds were analyzed in various solvents. The compounds formed stable gel in some of the solvents tested. The stability of the gels in acidic condition (pH 1) were also tested by adding sulfuric acid to the gels formed. The gel formed by the compounds dissolved at various rate. The gel formed by compound 39 dissolved after 2 hours while compound 40 dissolved after 6 hours. The dissolution of the gels is due to the p-methoxylbenzylidene acetal protecting group in the compounds that is acid labile.

In another report, Zhou and co-workers also reported the pH responsive supramolecular hydrogelator based on N-acetylgalactosamine Figure 20.79

![Figure 20](https://example.com/image.png)

**Figure 20.** Compound 41 and pH responsive compounds 42 and 43.

The physical state of the compounds changed from gel-to-sol upon pH variation. Compound 41 responded to variation in pH when mixed with an appropriate amount of amphiphilic carboxylic acid derivatives 42 or 43. It is important to note that pH variation has no effect on 41 by itself. However, when the gel was made from an equimolar mixture of 42 and 43, the volume of the gel shrinks upon pH variation.
1.4.2 EFFECT OF SALT ON GELATION

Bhattacharya described the effect of the addition of salt on the kinetics of gelation as well as the morphology of the gels. Figure 21 shows the structure of compounds whose gelation were influenced by the addition of salt. While compound 44 formed hydrogel, 45 did not form a gel. 44 retained its gelation ability at a pH range of 4-10.

![Chemical structures of compound 44 and 45.](image)

The kinetics of gelation was influenced by the addition of NaCl (1mM), KCl (1mM), CaCl$_2$ (1 mM) and MgCl$_2$ (1 mM) respectively to the gel formed by 44. The addition of salt to the aqueous phase delayed the gelation of the compounds. The morphology of the gels was also affected by the addition of salt. The gelation of 44 can be due to the hydrogen bonding and π-π interaction of the azobenzene group.
1.4.3 UV RESPONSIVE SYSTEMS

Over the past few decades, the preferential treatment of targeted disease such as cancer cell without causing any damage to the healthy cell continues to be a challenge. This is because many drugs are not able to distinguish between healthy cells and cancer cells. Consequently, there is a need to develop a delivery system that would ensure that the drug is release precisely at the target site (cancer cell).\textsuperscript{81-83} Great efforts have been made for decades to overcome this challenge including the use of light. The application of light for targeted disease treatment is not unconnected to its various advantages including the rare ability to control the amount of exposure, the ability to control the amount of drug released, the control of the location where the drug is released and the timing of the drug released.\textsuperscript{84-88} These advantages of light over other stimuli responsive methods have prompted many studies on the synthesis of light responsive compounds.

1.4.3.1 NITROPHENYL SYSTEM

Recently in 2015, Almutairi group synthesized a polymer that is responsive to UV light.\textsuperscript{89} The UV-responsive copolymer contains a carboxylic acid protected by 4,5-dimethoxy-2-nitrobenzyl alcohol protecting group, photo-responsive group and a ketal group. The polymer was observed to degrade after UV irradiation (1.35 mW) for about 5 mins at neutral pH by de-protecting the acidic group in the polymer backbone to enhance the hydrolysis of the ketal functional group. Figure 22 shows the structure of the photodegradable polymer.

The rate of degradation of the polymer, 46 was monitored using \textsuperscript{1}H NMR by observing the ketal peak. For the UV studies, two solutions of the polymer was prepared: first, a solution of the polymer in deuterated DMSO and deuterated phosphate buffer solution at pH 7.4 was prepared;
secondly, another solution of the polymer was prepared in deuterated DMSO and deuterated phosphate buffer solution at pH 5. The choice of DMSO for making the solution was not unconnected to the fact that DMSO was used to stabilize the polymer prior to UV irradiation. After UV irradiation, the polymer was observed to degrade in pH 7.4 by 55% faster than in pH 5 solution without irradiation. **Scheme 1** shows the degradation of the polymer.

![Scheme 1](image)

**Figure 22.** Structure of UV light degradable polymer 46.

The treatment of cancer cells by theranostic drug delivery systems (DDSs) have also received great attention recently. This is because of their inherent properties of combining two vital features: imaging and precise control over delivery of anti-cancer drugs. One of the disadvantage of photo-responsive drug delivery systems includes the accidental release of the drug when exposed to ambient light. Hence, to overcome this problem, the importance of locking the photo-trigger became more pertinent.

In 2015, Singh group reported the synthesis and analysis of a locked photo-responsive compound that has application for drug delivery. The synthesis of the locked photo-responsive compound, 58, is described in Scheme 2. Using vanillin and resorcinol as starting material, compound 54, o-nitrobenzylbromide derivative was synthesized in four steps from vanillin while compound 57, the prodrug was synthesized from resorcinol in two steps respectively. Using Williamson ether synthesis, compound 58 was synthesized by coupling both compounds 54 and 57. It can be observed that compound 58 is made up of two different responsive groups: the coumarin-based
light-trigger (prodrug) and the o-nitrobenzyl-based photo-trigger that is used to lock the coumarin-based photo-trigger. The o-nitrobenzyl-based photo-trigger has greater release ability than the coumarin-based photo-trigger.

The fluorescence turn on ability of compound \textbf{58} and the rate of cellular uptake were investigated by in vitro examination. The locked photo-caged compound \textbf{58} was tagged with 50 µM biotin to afford compound \textbf{59}, \textbf{Figure 23}. Breast cancer cells (MDA-MB-231) was used for the analysis. The incubation of the breast cancer cells (MDA-MB-231) was done using 4',6-diamidino-2-phenylindole (DAPI) and compound \textbf{59} for 4 hours. After irradiation of the incubated breast cancer cell with UV light at 365 nm, the fluorescent emission spectra showed that after 5 mins, the cancer cell glowed fluorescent green. This confirmed that the non-fluorescent compound \textbf{58} had been unlocked thereby releasing the fluorescent prodrug, coumarin-based photo-trigger which was responsible for the fluorescent observed. The fluorescent intensity was observed to increase with time as more of the uncaged fluorescent prodrug was released after 20 mins.

Moreover, the effect of UV light on compound \textbf{58} was also monitored using $^1$H NMR. NMR analysis showed that the irradiation of UV light on compound \textbf{58} after 5 mins lead to the formation of nitrosobenzaldehyde and the fluorescent prodrug. The formation of the nitrosobenzaldehyde was confirmed by the new peak at 9.67 ppm in $^1$H NMR.
Scheme 2. Synthesis of compound 58, dually locked photo-caged compound.

Figure 23. Structure of compound 59, biotin tagged dually locked photo-caged compound.
In another report by Almutairi in 2010, a light responsive polymer with light responsive groups along the backbone was developed. A nanoparticle was formulated from this light responsive polymer and was analyzed for the encapsulation and release of drug after light irradiation. The Scheme for the synthesis of the light responsive polymer is shown below (Scheme 3).

**Scheme 3.** Synthesis of compound \( \text{61} \)

After the copolymerization of compound \( \text{60} \) with adipoyl chloride to afford the polymer \( \text{61} \), the crude polymer was purified by washing it repeatedly with cold ethanol to afford the final product (44% yield) of 65,000 Da and PDI of 1.54. The PDI was calculated using GPC with polystyrene as standard. The effect of UV irradiation on the compound was monitored using UV-Vis analysis. A solution of the polymer in a mixture of acetonitrile and water (9:1) was irradiated with UV light at 750 nm for 15 mins. After 15 mins, the 4,5-dimethoxy-2-nitrobenzyl carbamate peak at 346 nm was observed to decrease while a new peak corresponding to the cleaved 4,5-dimethoxy-2-
nitrosobenzaldehyde was observed at 400 nm showing that the compound is responsive to UV light.

1.4.3.2 COUMARIN SYSTEM

In 2013, Zhu’s lab described the synthesis and characterization of a photo-responsive nanoparticle with both inherent and external controls. The inherent control is a tumor hypoxia that unlocks the nanoparticle while the external control is via light. The merits of this systems includes precise loading of the anticancer drug to the exact site of action since the inherent control prevents accidental discharge and deep tissue penetration. This system was based on the principle that nitroaromatics can be reduced to aminoaromatics in an oxygen deprived tumor cell (hypoxic tumor cell), thereby activating the compound. Figure 24 shows the two compounds that were used in this study. The compounds consist of a phototrigger or a hypoxia agent, a coumarin light responsive group and a caged drug. The drug used in this study was etoposide, the first topoisomerase inhibitor. The photo-trigger coumarin containing the nitroamino derivative is locked and hence has a weak fluorescence. The nitroimadozole on compound 62 acts both as a hypoxic agent and as an electron transfer agent. Fluorescence analysis was used to confirm that compound 62 was indeed locked as its fluorescence was very weak. This is because of the presence of the nitro group in compound 62. However, when the nitro group was reduced to the amino form, compound 63 using Na₂S₂O₄, the fluorescence ability of the coumarin in compound 63 was restored. The photolytic analysis was also carried out using HPLC. Both compound 62 and 63 were irradiated with a visible light of 500 W lamp, > 400 nm. HPLC analysis showed that compound 62 did not decompose after light irradiation for 20 mins. However, the unlocked photo-responsive compound 63 underwent photolysis after 20 mins as shown in Figure 25 to produce the prodrug. The by-
product of the photolysis is CO$_2$. The drug was eventually cleaved from the prodrug in physiological condition (0.1 M phosphate buffered saline) at 37 °C.

Figure 24. Structure of compounds 62 and 63.

Figure 25. Mechanism for the release of drug from the photo-trigger compound.
1.4.3.3 OTHER PHOTOLABILE SYSTEM

The cleavage of covalent bonds in photolabile protecting groups (PPGs) especially under mild conditions and in the absent of chemical reagents has make light controlled covalent bond breaking appealing to various research aspect. The application of PPGs include in organic synthesis, polymer science, surface patterning and photolithographic preparation of biochips.\textsuperscript{94-100}

The importance of carbonyl groups in organic synthesis cannot be over-emphasized and often needs to be protected in a many step syntheses. Hence, there has been a continuous effort towards the design of photolabile protecting groups for carbonyl for over four decades.\textsuperscript{101,102} In 2007, Wang group developed a novel photolabile protecting model for carbonyl groups by using 5-methoxysalicyclic alcohol derivative.\textsuperscript{103} The protected carbonyl group was in the form of a cyclic ketal or acetal as shown in Scheme 4.

\textbf{Scheme 4.} Protection of carbonyls with 5-methoxysalicyclic alcohol derivative.

The protection step was used for both aromatic and aliphatic aldehyde compounds. It is important to note that anhydrous CuSO\textsubscript{4} or P\textsubscript{2}O\textsubscript{5} were used as dehydrating agents for the protection of
ketones. A solution of the acetal in acetonitrile underwent photolysis in the presence of air to produce the carbonyls in a smooth way using a 450 W medium-pressure mercury lamp equipped with Pyrex filter sleeve.

The application of UV light for breaking benzylic C-O bond for PPG development started in the early 1960s\textsuperscript{104,105} as shown in Scheme 5. Barltrop and Schofield group reported the photochemical cleavage of N-benzyloxycarbonyl (Cbz) protected glycine to produce the corresponding benzyl alcohol after the hydrolysis of the intermediate product. However, the drawback to this protecting group is its poor stability under acidic condition. Following this chemistry, the protection of alcohols using PPG with increased stability under acidic condition became pertinent. The protection of alcohols using 3-dimethylaminotrityl groups (DMATr) was investigated by the Wang group.\textsuperscript{95} The meta group in compound 70, Figure 26 helped in improving the photochemical cleavage to afford the corresponding alcohol via excited state meta effect. Compound 70 also has a higher stability under acidic condition.

\textbf{Scheme 5}. PPG s featuring benzylic C-O bond cleavage.
The application of the 3-dimethylaminotrityl groups for the protection of amino groups was further investigated. Irradiation of a 6.0 mM solution of compound 71 in methanol for 15 min produced the intermediate product, 72 that was then reacted with 13 equiv of butyl amine to produce the secondary amine product 73 as shown in Scheme 6. It is important to note that the irradiation of a 5.0 mM solution of compound 73 in CD$_3$OD was observed to be yield no product (Scheme 7). This means that the DMATr PPG on amino groups is photochemically inactive.

Scheme 6. C-N bond formation via Photochemical methods

Scheme 7. Effect of UV light on compound 73.
However, the photo-chemically otherwise stable benzylic C-N bond in compound 73 can be compromised to enhance its cleavage by converting it to a photolabile bond. Treatment of compound 73 with HCl produced the stable compound 74. The stability of the C-N bond in compound 74 was confirmed even in excess HCl using $^1$H NMR analysis. The irradiation of compound 74 for 6 min produced the amine product, 75 in 81% yield (Scheme 8).

Scheme 8. C-N bond cleavage via photochemical methods.

1.4.3.4 DIACETYLENE SYSTEM

Gelators containing diacetylene functional group have received attention as intelligent sensing materials. They have the ability to show interesting optical and electronic properties after UV irradiation. These diacetylene containg compounds also exhibit color change from blue to red in response to UV treatment.$^{107,108}$ Wang group described the gelation properties of amphiphilic and bispolar diacetylene-containing glycolipids whose property changes after UV irradiation Figure 27.$^{76}$
Both compounds synthesized formed gel in at least two of the organic solvents tested but did not form gel in water. Studies showed the polymerization of the gels formed by compound 76 and 77 when exposed to a 6W TLC illuminating UV lamp at a wavelength of 254 nm. Polymerization of the gel was indicated by color change as the color changed from colorless to deep blue after 30 s UV irradiation. The opaque gel formed by compound 76 turned blue after treatment with UV for less than 10 mins. The gel further turned purple-red after being heated at 70 °C. The gel formed by 77 also experienced color change from colorless to blue after treatment with UV. The blue polymerized gel underwent further color transformation to red when heated in a water bath at 70 °C. Another noticeable difference in the physical property of the gels before and after UV treatment is their melting point. The melting point of the polymerized gels were higher than the un-polymerized gel showing that the polymerized gels were more stable. The morphology of the gels were also studied. Optical images showed that there was no significant difference in the morphology of the gels before and after UV irradiation except for color change.
In another report, Wang group also synthesized a series of diacetylene-containing glycolipids with ester linker whose property changes after UV irradiation. The gelation properties of the compounds were tested in hexane, ethanol and ethanol-water mixture. While 78 formed gel in ethanol at 5 mg/mL, 79 formed gel in ethanol-water mixture. Compound 80 was able to form gel in both hexane and ethanol solvents. The gel formed by 80 in hexane was polymerized when treated with 254 nm UV light.

**Figure 28.** Structures of diacetylene-containing ester derivatives 78-80.
The exposure of the gels to UV light for about one minute caused the gels to polymerize resulting in a color change to blue. The reversible polymerized blue gel turned red on heating and then reverted back to blue when cooled to rt. This color change from blue to red is reversible especially if the gel is heated below 70 °C.

1.4.3.5 AZOBENZENE SYSTEM

Oriol and co-worker reported the synthesis of a light responsive maltose-based gelators having an azobenzene, Figure 29. The gelation properties of the compounds were tested in various solvents including toluene, chloroform, THF, dodecanol, acetone, DMF, DMSO, methanol, water and DMSO:water solution. Compound 82 only formed gel in DMSO:water (1:1 w/w) at 2.0 wt%. while 81 formed gel in both water and DMSO:water (1:1 w/w) at 5.0 wt% and 1.5 wt% respectively.

Figure 29. Maltose-based gelators having an azobenzene.
1.5 APPLICATION OF LOW MOLECULAR WEIGHT GELATORS

Low molecular weight gelators have gained a wide range of application including in lubrication industry,\textsuperscript{18} sensors,\textsuperscript{110} wound healing,\textsuperscript{111} and waste treatment.\textsuperscript{112} There have been many reports on the selective gelation of oil-water mixtures using LMWGs especially because of the numerous cases of environmental pollution due to accidents when transporting crude oil. In 2014, Yadav and co-workers synthesized compound 83 (Figure 30) as a potential phase selective organogelation (PSOG) of crude oil.\textsuperscript{113} The gelation ability of both the D/L-83 was tested in various solvents including benzene, toluene, o-xylene, m-xylene, p-xylene. Others were chloroform, nitrobenzene and hexane. The compound formed gel in all of the solvents except in nitrobenzene. Gelation studies showed that both D/L-83 were able to form gel in petrol and diesel. D-83 formed gel in crude oil at a concentration of 0.5% (w/v). The gelation ability of 83 in a mixture of crude oil and saline water was studied. In this study, the addition of a concentrated petroleum solution of 83 to the mixture was observed to selectively gelate crude oil.

![Structure of organogelator D/L of compound 83.](image)

In another report, Sureshan and co-workers synthesized a sugar-based gelator for marine oil spill recovery.\textsuperscript{114} This system relied on the gelator property in which many alkyl 4,6-O-benzylidene-glycopyranosides are able to gelate in nonpolar solvent.\textsuperscript{48} Research shows that the acetal protection and the alcohol play a role in gelation. Compounds 84-88 were synthesized and their
gelation property were tested in both nonpolar solvent and water (Figure 31). The compounds did not form gel in water but were able to form gel in silicon oil, pump oil, and diesel. Their gelation ability increased with increasing the chain length of R group. This may be due to increase in the van der Waal interaction in the self-assembly process.

![Organogelator structure](image)

**Figure 31.** Structure of organogelator 84-88

Just recently, Yadav group reported a series of arabinose-based gelators with phase selective organogelation property **Figure 32**. The synthesis of the final product was a four step process starting from the conversion of D-arabinose to the per-O-acetylated derivative followed by the bromination of the anomeric position using PBr₃. The bromide was displaced with azide using sodium azide.
The final products, compounds 89 and 90 were finally synthesized via click chemistry. The gelation property of the compounds was tested in various solvents and it was found that both compounds formed gel in hydrocarbon based solvents including benzene, toluene, xylene, chlorobenzene, ethanol, kerosene, petrol and diesel. Compounds 89 and 90 formed supergelators in diesel and petrol as they both have a minimum gelation concentration of 0.3%, w/v. The phase selective organogelation (PSOG) of the compounds were analyzed in a two phase system containing water. The gelation ability of the compounds in a mixture of crude oil and saline water was studied. In this study, the addition of a concentrated petroleum solution of 89 to the mixture was observed to selectively gelate the crude oil.

The search for the treatment of cancer continues to be a burden to the world as cancer is the second leading cause of death. The treatment of cancer via chemotherapy and radiotherapy has been reported to cause side effects. Moreover, the poor solubility of most anti-cancer drugs meant that a delivery system is needed to transport the anti-cancer drug to the target site. Examples of such delivery systems are hydrogels, micelles, dendrimers, liposomes and nanoparticles. The use
of sugar-based low molecular weight hydrogels as a delivery system for anti-cancer drugs has attracted great attention for over two decades because it is biodegradable, biocompatible, has higher drug loading content and it is easily prepared.\textsuperscript{121,122} Moreover, the ability of low molecular weight hydrogels to be used for controlled and sustained released of anti-cancer drug make them an ideal delivery system for anti-cancer drugs.

In 2006, John group reported the synthesis of a sugar-based hydrogel using amygdalin derivative.\textsuperscript{28} The hydrogelator formed self-assembly to form nanoparticles which has potential of encapsulating a drug. The synthesis of the gelator is shown in Scheme 9

\textbf{Scheme 9.} Scheme for the synthesis of amygdalin ester.

The hydrogel formed by compound 92 was used in encapsulating a hydrophobic drug, curcumin and the rate of release of the drug from the gel matrix was controlled via varying the concentration of hydrolase enzyme (lipolase) and or temperature. When the hydrogelator was exposed to lipase, the hydrogelator was observed to degrade and thus releasing the encapsulated drug. The products of the enzymatic reaction are amygdalin, curcumin and enzymes.
Feng group described the design of a new series of coumarin-based fluorescent hydrogelators.\textsuperscript{123} The synthesis of these coumarin-based fluorescent hydrogelators from commercially available compounds in a one-step reaction were in good yields. The synthesis of the compounds are shown in Scheme 10. The compounds are comprised of three groups: pyridine, ester and coumarin groups. Interestingly, all the compounds are good gelators in water with compound 97 being the most effective gelator as shown in Table 1. The transition temperatures from gel to sol of the hydrogelators were determined also as shown in Table 1.

**Scheme 10.** Synthesis of a series of coumarin-based hydrogelators.

![Scheme 10](image)

**Table 1.** The transition temperature (TT) from gels to sol and minimum gelation concentration (MGC) of the hydrogelators

<table>
<thead>
<tr>
<th></th>
<th>TT</th>
<th>MGC (mg/mL)</th>
</tr>
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<tbody>
<tr>
<td>94</td>
<td>82</td>
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<td>10.4</td>
</tr>
<tr>
<td>97</td>
<td>87</td>
<td>2.8</td>
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<tr>
<td>98</td>
<td>95</td>
<td>12.5</td>
</tr>
<tr>
<td>99</td>
<td>93</td>
<td>4.7</td>
</tr>
</tbody>
</table>
The gelators were observed to be responsive when irradiated with UV light at 365 nm, emitting a blue light. Single crystals of compound 94 were formed using a solvent mixture of methanol and chloroform in other to understand the mechanism for self-assembly. From the crystal structure and the packing diagram, it was observed that the two non-conventional intermolecular hydrogen bonds (C-H…O=C) played a critical role in promoting self-assembly.

1.6 CONCLUSION

Research in the field of low molecular weight gelators continues to attract great attention due to their potential application in diverse research fields. They have been explored as vehicles for drug delivery, as sensors and in catalysis, tissue engineering and wound healing.

The design and synthesis of sugar based low molecular weight gelators have been on the increase for decades now because of the various advantages associated with carbohydrate such as their biocompatibility, biodegradable and they are easily prepared. As more research is done in understandings the mechanism of low molecular weight gelators, supramolecular gels may provide us with the necessary tools for solving a myriad number medical challenges including the development of improved therapeutic agents and delivery systems for treating disease and the protection of our environment. The potential applications of low molecular weight gelators are only limited by our thinking.
CHAPTER 2
SYNTHESIS AND GELATION PROPERTY STUDY OF A SERIES OF PERACETYLATED DISACCHARIDE TRIAZOLE DERIVATIVES

PREFACE

This chapter is adapted from the following publication:


2.1 INTRODUCTION

The synthesis and characterization of functional molecular assemblies formed by small molecules has gained much attention in recent years. Low molecular weight gelator (LMWGs) which is one class of functional molecular assemblies are a class of small molecules that are able to self-assemble and form reversible gels in organic solvents or aqueous solutions. These LMWGs can be classified as organogels or hydrogels if the gels are formed in organic solvent or in water respectively. These small molecular gelators can lead to the formation of soft gel materials through non-covalent interactions such as π-π stacking, hydrogen bonding, hydrophobic interactions, van der Walls forces, etc. The gels formed by LMWGs are usually reversible yet stable physicals gels or supramolecular gels because of the collectively weak non-covalent interactions.

Previous studies in the area of molecular gelators from the literature have shown that compounds containing some functional groups including alcohols, ureas, esters, carboxylic acids, triazole and
amides can influence gelation. The hydrogen bonding in these functional groups are especially responsive for gelation.\textsuperscript{130,131} Moreover, previous reports have also shown that compounds of biological origin and natural products including carbohydrates, amino acids and peptides have been reported to be effective gelators and have been found to be invaluable compounds in the field of soft materials and biomedical chemistry.\textsuperscript{132-136}

Among the various natural products, the natural abundance, biocompatibility and structural diversity of carbohydrates makes carbohydrate of interest to our group.\textsuperscript{32} The presence of free hydroxyl groups in carbohydrate can be regioselectively functionalized to afford diverse carbohydrate derivatives that could self-assemble forming supramolecular structures and sugar based LMWGs.

In 2001, Sharpless group pioneered the concept of click chemistry for the effective design of diverse compound libraries.\textsuperscript{137} The importance of “Click chemistry”, Cu (I) catalyzed azide-alkyne 1,3-dipolar cycloaddition reaction (CuAAC) in biochemistry and glycoscience cannot be over emphasized as it has been used extensively for the design of novel scaffolds and in material chemistry.\textsuperscript{138-140} The biological applications of triazole containing carbohydrate compounds including antibacterial and antiviral activities have led to an extensive synthesis of a number of carbohydrate based triazoles. Derivatives of tetrahydroprotoberberine (THPB) triazole have been reported to be active against micrococcus leteus and candida albicans.\textsuperscript{141} There have also been reports on the design of triazole based low molecular weight gelators.\textsuperscript{19,35,38} Our group has done extensive research on the functionalization of carbohydrate derivatives to obtain effective low molecular weight gelators over the past decade.\textsuperscript{27,36} Previously, we have reported the design and
synthesis of diverse derivatives of 4, 6-benzylidene acetal protected monosaccharides and found that they are effective sugar based LMWGs (Figure 33).\textsuperscript{27,31} The amide and urea derivatives obtained from D-glucosamine with the general structure 1 and 2 were reported to be good gelators in various solvents and aqueous mixtures. In 2015, our group reported the synthesis and characterization of a series of peracetylated glucosyl triazole derivatives and D-glucosamine triazole analogues with the general structure 3 and 4 using click chemistry.\textsuperscript{19} Different derivatives of the peracetylated glucosyl triazole and D-glucosamine triazole analogues were designed including long chain hydrocarbon tail, aromatic substituent, long and short chain alcohol derivatives and long chain carboxylic acid derivative. The gelation ability of the compounds was tested in various solvents such as hexane, IPA, toluene, water, ethanol and a mixture of ethanol-water and DMSO-water. Gelation test result shows that most of the carbohydrate based triazole derivatives were effective organogelators as they formed gel in a number of polar solvents and aqueous solutions. A few derivatives also formed an effective and stable hydrogel. Following these results, we are inquisitive to study the effect of extending the monosaccharide derivatives to disaccharide derivatives on gelation. For this study, lactose and maltose, the two most common commercially available disaccharides were used. We attempt to also expand on the library and scope of sugar based triazole low molecular weight gelators by extending the monosaccharides to disaccharides. Systematic studies of the disaccharide derivatives will also allow us to obtain structural features necessary for gelation. Systematic analysis on peracetylated disaccharide triazole analogs as molecular gelators have never been carried out yet as only a few disaccharide based triazole containing glycolipids have been reported to be effective supramolecular hydrogelators.\textsuperscript{59,60} This chapter will discuss the influence of extending the sugar moiety from
monosaccharide to disaccharide on gelation especially as our previous study showed that peracetylated glycosyl triazole lipids were effective molecular gelators.

Figure 33. Structures of glucosyl triazoles that are effective LMWGs and the proposed peracetylated disaccharide triazole derivatives.

2.2 RESULTS AND DISCUSSION

SYNTHESIS OF PERACETYLATED DISACCHARIDE β-1,2,3-TRIAZOLE DERIVATIVES

In an effort to gain a better understanding on the structural requirement for gelation, we aim to extend the monosaccharide triazole system to disaccharide triazole systems and determine if the additional monosaccharide will affect the molecular self-assembling behavior of the gelators in different solvents including non-polar, polar and aqueous solutions. Lactose and maltose, two of the most common disaccharide compounds were selected for the study. As shown in Scheme 11,
the lactose triazole headgroup 5 and maltose triazole headgroup 6 (Scheme 12), are analogs of the glucosyl triazoles and are both synthesized from lactose and maltose respectively in three steps.

Lactosyl azide 10 was synthesized following literature methods using the lactose as the starting materials (Scheme 11). The first synthetic step was the conversion of lactose 7 to the peracetylated compound 8 with the beta isomer as the major product. The acetate on the anomeric position of compound 8 was converted to bromide to afford compound 9 in good yield, followed by azide displacement of the bromide in compound 9 to afford the compound 10. The lactose based triazole derivatives, 11-19 were prepared via click chemistry by reacting the peracetylated sugar azide 10 with the corresponding terminal alkynes with different functional groups respectively using catalytic amount of copper sulphate and sodium ascorbate. The gelation ability of the derivatives including the short alkyl chain derivatives 11-12, chlorobutyl analog 13, terminal hydroxyl 14-17, carboxylic acid derivative 18 and phenyl derivative 19 were studied in different solvents as shown in Table 2. The crude products of all the synthesized derivatives were purified by column chromatography on silica gel using a gradient of 0.5% MeOH/DCM to 5% MeOH/DCM.

The gelation test result showed that none of the peracetylated lactosyl triazole derivatives formed gel in the tested solvents. The gelators were mostly soluble in polar solvents (alcohol), insoluble in non-polar solvents (hexane) and formed a precipitate in the other tested solvents including in aqueous solutions. Only Compound 19, the phenyl derivative was able to form a gel in aqueous solutions of DMSO:water and EtOH:water. The gelation ability of compound 19 may be attributed to the \( \pi-\pi \) stacking interactions from the phenyl functional group.
**Scheme 11.** Synthesis of peracetylated lactosyl triazole derivatives.

\[
\begin{align*}
\text{Scheme 11.} & \quad \text{Synthesis of peracetylated lactosyl triazole derivatives.} \\
7 & \xrightarrow{\text{NaOAc, Ac₂O, reflux 4 hrs}} 95\% \quad 8 \\
9 & \xrightarrow{\text{NaN₃, DMF, 70 °C}} 87\% \quad 10 \\
5 & \xrightarrow{\text{CuSO₄, sodium ascorbate, t-BuOH: THF: H₂O (1:1:1), rt, 24 h}} \quad R \\
11 & 80\% \\
12 & 76\% \\
13 & 79\% \\
14 & 87\% \\
15 & 75\% \\
16 & 70\% \\
17 & 75\% \\
18 & 84\% \\
19 & 85\%
\end{align*}
\]
Table 2. Gelation test results for lactosyl triazole derivatives with the general structure of 5

<table>
<thead>
<tr>
<th>Compound number</th>
<th>Hexane</th>
<th>Toluene</th>
<th>i-PrOH</th>
<th>EtOH</th>
<th>H2O</th>
<th>DMSO: H2O (1:1)</th>
<th>DMSO: H2O (1:2)</th>
<th>EtOH: H2O (1:1)</th>
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<tr>
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<td>S</td>
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<td>P</td>
<td>G 10</td>
<td>UG</td>
<td>G 5.0</td>
</tr>
</tbody>
</table>

G, gel at room temperature; the number in the table are the minimum gelation concentrations in mg/mL; I, insoluble; P, precipitate; UG, unstable gel; S, soluble at 20 mg/mL; UG, unstable gel.

After successfully synthesizing the lactosyl triazole derivatives, we then set forth our attention to the synthesis of another common disaccharide based triazole, the maltosyl triazole derivatives, which have two glucose unit linked by α (1-4) glycosidic bond. The maltosyl triazole derivatives were synthesized using a similar series of alkyne as shown in Scheme 12. Including straight chain alkyl analogs 24-26, chlorosubstituted alkyl derivative 27, terminal hydroxyl derivatives 28-31, carboxylic acid derivative 32, and aromatic derivatives 33-34.

The gelation abilities of these compounds were then examined in a similar solvent series as with the lactosyl derivatives. The gelation test results are shown in Table 3. From Table 3, it was observed that most of these peracetylated maltosyl triazole derivatives were effective gelators for at least one of the tested solvents, in contrast to what was obtained with the lactosyl derivatives. The gelation ability of the maltosyl triazole derivatives resembles those of the monosaccharide glucosyl derivatives. Two dimeric triazole analogs 35 and 36 were also synthesized via click chemistry and their gelation properties were also evaluated as shown in Table 3. The dimeric compounds were however not as effective as the monomeric derivatives.

Table 3. Gelation screening results for maltosyl triazole derivatives.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hexane</th>
<th>Toluene</th>
<th>i-PrOH</th>
<th>EtOH</th>
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<th>DMSO: H₂O (1:1)</th>
<th>DMSO: H₂O (1:2)</th>
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<td>S</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>G 4.0</td>
<td>G 4.0</td>
<td>G 3.3</td>
</tr>
<tr>
<td>25</td>
<td>I</td>
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<td>S</td>
<td>S</td>
<td>S</td>
<td>G 2.8</td>
<td>G 2.8</td>
<td>G 5.0</td>
</tr>
<tr>
<td>26</td>
<td>I</td>
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<td>P</td>
<td>G 10</td>
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<td>27</td>
<td>I</td>
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<td>G 20</td>
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<tr>
<td>28</td>
<td>I</td>
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<td>G 20</td>
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<tr>
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<td>I</td>
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<td>P</td>
<td>S</td>
<td>G 10</td>
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<tr>
<td>31</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<td>G 5.0</td>
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<tr>
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<td>I</td>
<td>S</td>
<td>S</td>
<td>G 5.0</td>
<td>I</td>
<td>G 4.0</td>
<td>G 2.0</td>
<td>G 3.3</td>
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<tr>
<td>34</td>
<td>I</td>
<td>S</td>
<td>G 10</td>
<td>G 10</td>
<td>P</td>
<td>G 4.0</td>
<td>G 4.0</td>
<td>G 5.0</td>
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<td>P</td>
<td>P</td>
</tr>
<tr>
<td>36</td>
<td>I</td>
<td>S</td>
<td>G 20</td>
<td>P</td>
<td>P</td>
<td>G 10</td>
<td>P</td>
<td>P</td>
</tr>
</tbody>
</table>

G, gel at room temperature; the number in the table are the minimum gelation concentrations in mg/mL; I, insoluble; P, precipitate; S, soluble at 20 mg/mL.
The gelation properties of the lactosyl triazole and maltosyl triazole derivatives were evaluated using different solvents including hexane, toluene, IPA, DMSO, ethanol, water and aqueous solution and the gelation test analysis are described in Table 2 and 3. The potential applications of hydrogels in drug delivery and biological studies meant that we were most interested in the gelation result in water and in aqueous solutions. These solvents used for the gelation study is also consistent with what we have used in our previous studies. The lactosyl based triazole derivatives designed with the general structure of 5 were poor gelators in the solvents tested as shown in Table 2. The poor gelation property of these triazole series may not be unconnected to the effect of the acetyl group on the axial position on the galactose ring. However, as shown in Table 3 the maltosyl based triazole derivatives of the general structure 6 were observed to be effective gelators. The effective gelation property of these maltosyl triazole series may not be unconnected to the second glucose ring of the maltose sugar. From previous report, we have observed that glycosyl based triazole is an effective gelator. As shown in Table 3, most of the derivatives of compound 6 were effective gelators in aqueous solution and ethanol. The derivatives however were poor gelators in hexane and toluene. Compound 34 and 36 formed gel in isopropanol while four compounds, 28, 33, 34 and 35 were effective gelators in ethanol. Only compound 30 formed a hydrogel while a good number of the gelators were effective gelators in a mixture of DMSO:H2O including compounds 24, 25, 27, 31, 32, 33, 34, 36. Similarly, a good number of the gelators were effective gelators in a mixture of EtOH:H2O including compounds 24, 25, 26, 32, 33, 34. The gelation ability of these compounds in the various solvents can be attributed to the presence of hydrogen bonding, π-π stacking and hydrophobic interaction. Hydrophobic interaction was more responsible for gelation in compounds 31 and 32 because of the long hydrophobic chain. However, the short hydrocarbon chain in compounds 28 and 29 meant that they were poor gelators.
The influence of the hydrophobic interaction in gelation was also responsible for effective gelation in compound 26 containing long aliphatic chain in aqueous ethanol solution while the shorter aliphatic chain derivatives 24 and 25 were effective gelator in all the aqueous solutions tested. The importance of π-π stacking in promoting gelation was responsive for the effective gelation result in compounds 33 and 34. The dimeric compounds 35 and 36 were not effective gelators.

Photographs of some of the gels formed by the maltosyl triazole series are shown in Figure 34. Most of the gels formed by the maltosyl triazole series are transparent while some of them are translucent.

Figure 34. The photos of the gels formed by the gelators 24 (A, B), 25 (C), 32 (D), and 33 (E). A: compound 24 in EtOH:H2O (v 1:2) at 3.3 mg/mL; B: compound 24 in DMSO:H2O at 4.0 mg/mL; C: compound 25 in DMSO:H2O (v1:2) 2.8 mg/mL; D: compound 32 in DMSO:H2O (v 1:2) at 2 mg/mL; E: compound 33 in EtOH:H2O (v 1:2) at 3.3 mg/mL.
The morphologies of the gels formed by compounds 24, 25, 32, 33, and 34 were studied using optical microscopy, these are shown in Figure 35. The gels formed by these various maltosyl triazole derivatives typically exhibited fibrous network. The gel formed by compound 24 in DMSO:H₂O (v 1:1) at 4.0 mg/mL exhibited very long and uniform fibrous assemblies, with length scale at several hundreds of microns (Fig. 35A), Fig. 35B showed the long fibers at higher magnifications, the fibrous diameters are estimated at 0.5 µm. In contrast, the hexyl analog compound 25 formed much shorter fibers in DMSO:H₂O (v1:2), with estimated lengths of 10-20 µm, and similar widths. Fig. 35D showed the gel morphology of compound 32 in DMSO:H₂O (v 1:2) at 2.0 mg/mL, this gel had very different features that they form continuous film with some fibrous structures. The gel morphology of the phenyl analog compound 33 in EtOH:H₂O (v 1:2) at 3.3 mg/mL exhibited two different morphologies ranging from smooth film (Fig. 35E) to tree branch like fibrous network (Fig. 35F); the compound 33 in EtOH at 5.0 mg/mL showed similar continuous film like aggregates (Fig. 35G); while the gel formed by compound 34 in EtOH:H₂O (v 1:1) at 5.0 mg/mL showed soft entangled fibrous networks (Fig. 35H).

The stability and elastic properties of the gels were also studied using rheology and the results are shown in Figure 36. For the gels formed by compounds 32, 31 and 24, their G’ storage moduli are greater than G” loss moduli. Compound 32 has the highest G’ and G” values among the three gels, indicating that the mechanical strength of the gel is the greatest among these three. But all the three gelators analyzed showed they formed stable and elastic gels.
Figure 35. Optical micrographs of the gels formed by compounds 24, 25, 32, 33, and 34. A, B: 
gel formed by compound 24 in DMSO:H₂O (v 1:1), 4.0 mg/mL at 10 µm; C, a gel from compound 
25 in DMSO:H₂O (v 1:2), 2.8 mg/mL at 10 µm; D: a gel formed by compound 32 in DMSO:H₂O 
(v 1:2), 2.0 mg/mL at 50 µm; E and F: compound 33 in EtOH:H₂O (v 1:2), 3.3 mg/mL at 50 µm;
G: compound 33 in EtOH, 5.0 mg/mL at 20 μm; H: compound 34 in EtOH:H₂O (v 1:1), 5.0 mg/mL at 20 μm.

In order to understand the molecular interactions and the self-assembling process, we performed ¹H-NMR studies at different temperatures for the gelator compounds with polar terminal substituents, 29, 31, 32 and phenyl derivatives 33, 34. These are shown in Figures 37-43. The ¹H-NMR spectra of compound 29 at temperatures ranging from 30 °C to 60 °C are shown in Figure 37 and Figure 38. When temperature is increased, the signal of the triazole proton shifted upfield from 7.49 ppm at 30 °C to 7.46 ppm at 60 °C. The splitting patterns of signals in 3.90-4.30 ppm (Figure 38) region have changed significantly; these are corresponding to the hydrogens on C-5 and C-6 of both sugars, these indicated that the disaccharide moiety is also very much contributing to the molecular assemblies. Besides these two main regions, other regions didn’t show noticeable changes. Similar trends were observed for the other three compounds, 31, 33 and 34. Compound 31 showed 0.02 ppm upfield shift when temperature is increased (Figure 39).

Compounds 33 and 34 also exhibited 0.02 ppm upfield change from 30 °C to 60 °C (Figures 40 and 41). Interestingly the compound with carboxyl functional group 32 didn’t follow the same trend at different temperature, the triazole signal stayed at 7.43 ppm for all tested temperatures. But the regions corresponding to the disaccharides on C-5 and C-6 from 3.90-5.60 ppm have changed significantly in splitting pattern and chemical shifts (Figure 42). We rationalize that at higher temperatures the chemical shift changes are due to the change of the van der Waals interactions among the sugar headgroup and the π-π stacking of the triazoles. This indicated that
the triazole ring’s \(\pi-\pi\) interactions are important for the molecule self-assembly and may impact the gelation behavior.

**Figure 36.** The rheological measurement of the gels formed at 5% strain by compound 24 (DMSO:H\(_2\)O, v1:1, 4 mg/mL), 31 (DMSO:H\(_2\)O, v1:2, 4 mg/mL) and 32 (DMSO:H\(_2\)O, v1:2, 2 mg/mL).
Figure 37. $^1$H NMR spectra at variable temperature of compound 29 from 30 °C to 60 °C in CDCl$_3$. 
Figure 38. $^1$H NMR spectra at variable temperature of compound 29 from 30 °C to 60 °C in CDCl$_3$ between 2.50 ppm and 4.50 ppm.
Figure 39. $^1$H-NMR spectra at variable temperature of compound 31 from 30 °C to 60 °C in CDCl$_3$. The triazole peak shifted from 7.42 at 30 °C to 7.40 ppm.
Figure 40. $^1$H-NMR spectra at variable temperature of compound 33 from 30 °C to 60 °C in CDCl$_3$. for full range.
Figure 41. $^1$H-NMR spectra at variable temperature of compound 34 from 30 °C to 60 °C in CDCl$_3$ for full range.
Figure 42. $^1$H-NMR spectra at variable temperature of compound 32 from 30 °C to 60 °C in CDCl$_3$ around 4 ppm.

We also acquired the $^1$H NMR spectra at the variable concentrations at 30 °C for compound 32, as shown in Figure 43. In contrast to the temperature dependent studies, the triazole ring showed a slight upfield shield at higher concentration. The upfield shift of the triazole $^1$H signal at higher concentration indicated that the glycosyl triazole compound self-assembles in solution via $\pi$-$\pi$ stacking.\textsuperscript{143}
Figure 43. $^1$H-NMR spectra at variable concentration of compound 32 in CDCl$_3$. The triazole peak shifted from 7.43 at 4 mg/mL to 7.42 ppm at 16 mg/mL.

**Drug release study**

The potential application of the gel formed by compound 33 for drug delivery was studied. A non-steroidal anti-inflammatory drug (NSAID) naproxen was used for this study and the release profile of the drug trapped in the gel matrix was determined. UV-Vis spectroscopy technique was used to monitor the rate of release of naproxen at room temperature. The gel formed by compound 33 was
selected for the study and the release profiles of naproxen drug from the gel matrix into the aqueous phase (pH 7 and pH 10) were monitored at different time intervals. The gel was prepared in a 1 dram vial using compound 33, 2 mg in 1.0 mL of a DMSO:H₂O (1:2) solution. Then 0.5 mg of sodium naproxen was added. After the formation of a stable gel, 3 mL of pH 7 solution was added on top of the gel and the estimated rate of release of naproxen into the aqueous phase was measured. (Figure 44). The release of naproxen from the gel matrix into the aqueous solution was monitored by UV absorption at various times. For naproxen released at pH 10, the gel was prepared in a similar way. After the formation of a stable gel, 3 mL of pH 10 solution was added on top of the gel and the rate of release of naproxen into the aqueous phase was measured. The release of naproxen from the gel matrix into the aqueous solution was also monitored by UV absorption at various times.

As shown in Figure 45 and 46, the rate of naproxen released from the gel matrix to the neutral aqueous phase varies depending on the pH of the aqueous phase. 95% of the naproxen drug was released into the aqueous phase after 72 h at pH 10 while 87% of the naproxen drug was released into the aqueous phase after 72 h at pH 7 (Table 4).
Figure 44. (A) is a gel formed when compound 33 (2 mg), naproxen sodium (0.5 mg) were dissolved in 1.0 mL DMSO:H$_2$O (1:2). 3 mL of pH 10 solution added on top of the gel. The picture shows that the gel is stable; (B) is the inverted picture of the gel after the addition of pH 10 solution. The gel pictures show that the gel is stable at pH 10. The gel picture is also similar for pH 7 solution.

The release of chloramphenicol trapped in a gel matrix formed by compound 32 was also examined using UV-Vis spectroscopy at varying pH solutions at different time intervals. Chloramphenicol is an antibiotic that is active against streptococcus and methicillin-resistant Staphylococcus aureus (MRSA). The gel was prepared in a 1 mL dram vial. Compound 32, 4 mg was dissolved in 0.9 mL of a DMSO:H$_2$O (1:2) solution of 0.2 mg of chloramphenicol. After the formation of a stable gel, 3 mL of pH 7 solution was added on top of the gel and the rate of release of chloramphenicol into the aqueous phase was measured (Figure 47). The release of chloramphenicol from the gel matrix into the aqueous solution was monitored by UV absorption at various time. For chloramphenicol released at pH 10, the gel was prepared in a similar way. After the formation of
a stable gel, 3 mL of pH 10 solution was added on top of the gel and the rate of release of chloramphenicol into the aqueous phase was measured. **Figure 48.** The release of chloramphenicol from the gel matrix into the aqueous solution was also monitored by UV absorption at various time.

**Figure 45.** UV spectrum showing the estimated amount of naproxen sodium released from the gel matrix formed by compound 33, 2 mg, naproxen 0.5 mg in 1.0 mL DMSO:H₂O (1:2) into the aqueous phase at pH 7.
Figure 46. UV spectrum showing the estimated amount of naproxen sodium drug released from the gel matrix formed by compound 33, 2 mg, naproxen 0.5 mg in 1.0 mL DMSO:H₂O (1:2) into the aqueous phase at pH 10.

As shown in Figure 49 and 50, the rate of chloramphenicol release from the gel matrix to the aqueous phase varies depending on the pH of the aqueous phase. 85% of chloramphenicol was released into the aqueous phase after 10 h at pH 10 while 54% of chloramphenicol was released into the aqueous phase after 10 h at pH 7 (Table 5). A higher amount of the dye was released at pH 10 because of the deprotonation of the carboxylic acid functional group in the gelator thereby causing a disruption in the gel matrix.
Table 4. Table showing the rate of release of naproxen drug to the aqueous phase at different pH solutions.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Estimated naproxen drug released (%) pH-10</th>
<th>Estimated naproxen drug released (%) pH-7</th>
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<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>13</td>
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<td>2</td>
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<tr>
<td>Naproxen standard in water</td>
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<td>100</td>
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</table>

Figure 47. (A) is a gel formed by compound 32 (4 mg) dissolved in 0.9 mL of a DMSO:H\textsubscript{2}O (1:2) solution of 0.2 mg of chloramphenicol dye. 3 mL of pH 7 solution added on top of the gel after 1 h; (B) is after 10 h; C and D is after 36 h. The picture shows that the gel is stable.
Figure 48. A is a gel formed by compound 32 (4 mg) dissolved in 0.9 mL of a DMSO:H$_2$O (1:2) solution of 0.2 mg of chloramphenicol dye. 3 mL of pH 10 solution added on top of the gel after 1 hour; B and C is after 24 h.

Figure 49. UV spectrum showing the estimated amount of chloramphenicol dye released from the gel matrix formed by compound 32, 4 mg, chloramphenicol dye 0.2 mg in 0.9 mL DMSO:H$_2$O (1:2) into the aqueous phase at pH 7.
**Figure 50.** UV spectrum showing the estimated amount of chloramphenicol dye released from the gel matrix formed by compound 32, 4 mg, chloramphenicol dye 0.2 mg in 0.9 mL DMSO:H₂O (1:2) into the aqueous phase at pH 10.

**Table 5.** Table showing the rate of release of chloramphenicol dye trapped in a gel matrix to the aqueous phase at different pH solutions.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Estimated chloramphenicol released (%) pH-10</th>
<th>Estimated chloramphenicol released (%) pH-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</tr>
<tr>
<td>Chloramphenicol standard</td>
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</table>
All the compounds were characterized using $^1$H NMR, $^{13}$C NMR, LCMS, HRMS and melting point. The $^1$H NMR, $^{13}$C NMR and HRMS spectra of some selected compounds are shown in Figures 51 and 52 respectively.

**Compound 12**

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**Figure 51**

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**Figure 52**
Figure 51. (A) $^1$H NMR; (B) $^{13}$C NMR and (C) LCMS spectra of compound 12.
Compound 28

A

B

79
Figure 52. (A) $^1$H NMR; (B) $^{13}$C NMR and (C) HRMS spectra of compound 28.

2.3 CONCLUSIONS

In summary, we have synthesized and studied two novel series of disaccharides triazole derivatives using maltose and lactose headgroups via click chemistry. The gelation studies of the various peracetylated disaccharide $\beta$-1,2,3-triazole derivatives in non-polar, polar and solvent mixtures were examined. We found that most of the peracetylated maltosyl $\beta$-triazole derivatives were effective low molecular weight gelators while the peracetylated lactosyl $\beta$-triazole derivatives were not effective gelators for the tested solvents. $^1$H NMR studies at different temperatures showed that the difference in gelation properties of the peracetylated maltosyl $\beta$-triazole and peracetylated lactosyl $\beta$-triazole derivatives was attributed to the configuration of the sugar moiety. Also, the influence of the various substituents on the triazole ring of the maltose derivatives was also examined. It was observed that the presence of aromatic substituent on the triazole ring promotes
gelation. Moreover, the long chain alcohol substituent also performed better than the short chain substituent. The improved gelation properties of the long chain alcohol derivatives can be attributed to the hydrophobic forces. $^1$H NMR studies at different temperatures showed that the triazole heterocycle played an important role in the molecular assemblies together with hydrogen bonding from polar substituents. The potential application of triazole based gelators for drug delivery was also studied using two gelator compounds, 32 and 33. UV-Vis spectroscopy showed that the compounds exhibited sustained release of the entrapped drug molecules especially at basic pH.

2.4 EXPERIMENTAL SECTION

**General methods:** All reactions were carried out under normal conditions, solvents and reagents were obtained commercially and used directly without any further purifications. Solvents and reagents were purchased from Sigma-Aldrich, VWR, and Fisher etc. All reactions, unless otherwise noted were carried out in oven dried glassware under nitrogen atmosphere. Chromatography was carried out using silica 100-200 mesh silica gel. Thin-layer chromatography (TLC) analysis was performed with Sigma-Aldrich silica gel Aluminum TLC plates, and visualized using UV lamp at 254 nm. $^1$H NMR and proton-decoupled $^{13}$C NMR spectra were obtained with Bruker 400 MHz spectrometers in CDCl$_3$. Proton and carbon spectra chemical shifts were reported using CDCl$_3$ as internal standard at 7.26 ppm and at 77.00 ppm respectively.

**Gelation testing:** In general, about 2 mg of the compounds were tested in a 1 dram vial with a rubber lined screw cap. To this vial, solvents were added in a 0.1 mL increment. A starting
concentration of 20 mg/mL was used. The mixture was heated and sonicated until the sample was fully dissolved. The mixture was then allowed to cool at room temperature for 30 mins. The vial was then examined visually. If it appears as a homogenous semi-solid, the vial was then inverted; and if after being inverted, no solvent flows, then the gel is called a stable gel. If the semi-solid like material fell apart while being inverted, it is called an unstable gel. A serial dilution is performed on the stable gel formed until the resulting gel is no more stable. The concentration prior to the formation of the unstable gel was recorded as the minimum gelation concentration (MGC).

**Optical microscopy:** A small amount of the stable gels was transferred to a clean glass slide using a spatula or pipette and was observed directly under an optical microscope. Some of the gels were left air dried for a few hours if too much liquid prevent imaging. The gels were observed using the 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 is CellSens 1.11.

**Rheological Analysis:** The elasticity and stability of the gels were determined using rheological analysis. The rheology experiment was performed on the HR-2 Discovery hybrid rheometer by TA instrument, operating in an oscillatory mode, with a 25 mm stainless steel parallel plate geometry. The Peltier temperature controller was set to maintain a temperature of 25 °C during the measurement. Typically, 0.5-1 mL of gels were transferred quickly to the center of the Peltier plate, the gel samples were analyzed immediately with a gap of 100 μm, and dynamic frequency sweep was performed from 0.1 to 100 rad/s with 5% strain.
A general procedure for the synthesis of triazole analogs. Hepta-O-acetyl-β-lactosyl azide 10, 100 mg was dissolved in 4.5 mL mixture of t-BuOH: H₂O: THF (1:1:1), the corresponding alkyne (1.2 mmol), copper sulphate (0.2 mmol) and sodium ascorbate (0.4 mmol) were also added. The reaction mixture was stirred at room temperature for 16 h. Reaction was monitored by TLC, NMR and LCMS. The mixture was concentrated and diluted with DCM and washed with water. The organic phase was dried over sodium sulphate, filtered and concentrated. The crude products were purified by flash chromatography on silica gel using a gradient of 0.5% MeOH/DCM to 5% MeOH/DCM. The yields of the isolated pure products and their characterization data are given for each compound. The same procedure was also used for the synthesis of the hepta-O-acetyl-β-maltosyl triazole derivatives, the starting material hepta-O-acetyl-β-maltosyl azide used was on a 50 mg scale. The yields of the isolated pure products and their characterization data are given for each compound.

For the ¹H NMR assignment, the labeling of the protons are:

1-(Hepta-O-acetyl-β-lactosyl)-4-butyl-1,2,3-triazole, compound 11 was obtained as a white solid, 79.7 mg in 80% yield, mp 156.0-158.3 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.40 (s, 1H), 5.79-5.77 (m, 1H), 5.39-5.33 (m, 3H), 5.09 (dd, J = 7.8, 7.9 Hz, 1H), 4.95 (dd, J = 3.4, 10.4 Hz, 1H), 4.51 (d, J = 7.8 Hz, 1H), 4.45 (dd, J = 10.6, 12.0 Hz, 1H), 4.15-4.05 (m, 3H), 3.96-3.87 (m, 3H), 2.68 (t, J = 7.7 Hz, 2H), 2.13-1.83 (m, 21H), 1.66-1.58 (m, 2H), 1.38-1.28 (m, 2H), 0.894 (t, J = 7.3
Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.2, 170.1, 170.0, 169.9, 169.4, 169.1, 169.0, 149.0, 118.7, 101.1, 85.3, 75.8, 75.6, 72.6, 70.8, 70.7, 70.4, 69.0, 66.6, 61.8, 60.8, 31.1, 25.2, 22.1, 20.7, 20.6, 20.5, 20.5, 20.4, 20.1, 13.7; HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{32}$H$_{45}$N$_3$O$_{17}$Na, 766.2641; found, 766.2632.

1-(Hepta-O-acetyl-β-lactosyl)-4-hexyl-1,2,3-triazole, compound 12 was obtained as a white solid, 88.9 mg in 76% yield, mp 94.0-96.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 (s, 1H), 5.80 (d, $J = 8.7$ Hz, 1H), 5.39-5.35 (m, 3H), 5.12 (dd, $J = 7.9$, 10.6 Hz, 1H), 4.96 (dd, $J = 3.4$, 10.4 Hz, 1H), 4.52 (d, $J = 7.9$, 1H), 4.47 (dd, $J = 10.6$, 12.4 Hz, 1H), 4.16-4.06 (m, 3H), 3.96-3.87 (m, 3H), 2.68 (t, $J = 7.9$ Hz, 2H), 2.17-1.82 (m, 21H), 1.66-1.62 (m, 2H), 1.33-1.28 (m, 6H), 0.90-0.83 (t, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.2, 170.1, 170.0, 169.9, 169.4, 169.1, 169.0, 149.0, 118.7, 101.0, 85.4, 75.8, 75.6, 72.6, 70.8, 70.8, 70.4, 69.0, 66.5, 61.7, 60.8, 31.4, 29.0, 28.7, 25.5, 22.4, 20.7, 20.6, 20.6, 20.5, 20.4, 20.1, 13.9; HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{34}$H$_{49}$N$_3$O$_{17}$Na, 794.2954; found, 794.2945.

1-(Hepta-O-acetyl-β-lactosyl)-4-(4-chlorobutyl)-1,2,3-triazole, compound 13 was obtained as a white solid, 95.1 mg in 79% yield, mp 93.5-95.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.44 (s, 1H), 5.77 (d, $J = 9.0$ Hz, 1H), 5.38-5.30 (m, 3H), 5.07 (dd, $J = 7.8$, 10.4 Hz, 1H), 4.93 (dd, $J = 3.4$, 10.4 Hz, 1H), 4.50 (d, $J = 7.8$ Hz, 1H), 4.44 (dd, $J = 10.8$, 12.0 Hz, 1H), 4.14-4.03 (m, 3H), 3.95-3.86 (m, 3H), 3.52-3.49 (m, 2H), 2.70 (t, $J = 6.6$ Hz, 2H), 2.11-1.82 (m, 21H), 1.80-1.77 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.2, 170.1, 170.0, 169.9, 169.3, 169.1, 168.9, 148.0, 118.9, 100.9, 85.3, 75.8, 75.5, 72.5, 70.8, 70.7, 70.4, 69.0, 66.5, 61.7, 60.8, 44.5, 31.7, 26.2, 24.7, 20.7, 20.6, 20.5, 20.5, 20.4, 20.1; HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{32}$H$_{44}$ClN$_3$O$_{17}$Na, 800.2251; found, 800.2241.
1-(Hepta-\textit{O}-acetyl-\textit{\-}\textbeta\textit{- lactosyl})-4-(hydroxylmethyl)-1,2,3-triazole compound 14 was obtained as a white solid, 86.5 mg in 87\% yield, mp 182.4-187.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71 (s, 1H), 5.84-5.82 (m, 1H), 5.41-5.36 (m, 3H), 5.13 (dd, $J = 7.9$, 10.4 Hz, 1H), 4.97 (dd, $J = 3.4$, 10.4 Hz, 1H), 4.79 (s, 2H), 4.53 (d, $J = 7.9$, 1H), 4.48 (dd, $J = 10.5$, 12.1 Hz, 1H), 4.18-4.07 (m, 3H), 3.99-3.89 (m, 3H), 2.16-1.88 (m, 21H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.3, 170.2, 170.1, 170.0, 169.5, 169.2, 169.0, 148.2, 120.1, 101.1, 85.6, 76.0, 75.6, 72.6, 70.9, 70.9, 70.6, 69.1, 66.6, 61.7, 60.8, 56.6, 20.8, 20.7, 20.6, 20.6, 20.5, 20.2; HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{29}$H$_{39}$N$_3$O$_{18}$Na, 740.2121; found, 740.2116.

1-(Hepta-\textit{O}-acetyl-\textit{\-}\textbeta\textit{- lactosyl})-4-(3-hydroxylpropyl)-1,2,3-triazole, compound 15 was obtained as a white solid, 84.9 mg in 75\% yield, mp 166.0-167.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49 (s, 1H), 5.79 (d, $J = 8.7$ Hz, 1H, H-1), 5.41-5.32 (m, 2H, H-2, H-3), 5.37 (d, $J = 4.8$ Hz, 1H, H-4'), 5.11 (dd, $J = 7.8$, 10.5 Hz, 1H, H-2'), 4.96 (dd, $J = 3.4$, 10.5 Hz, 1H, H-3'), 4.52 (d, $J = 7.9$ Hz, 1H, H-1'), 4.48-3.88 (m, 7H, H-4, H-5, H-6, H-5', H-6'), 3.65 (t, $J = 6.0$ Hz, 2H, CH$_2$(CH$_2$)$_2$OH), 2.82 (t, $J = 7.2$ Hz, 2H, (CH$_2$)$_2$CH$_2$OH), 2.29 (broad, 1H, CH$_2$CH$_2$CH$_2$OH), 2.14-1.85 (m, 21H), 1.95-1.90 (m, 2H, CH$_2$CH$_2$CH$_2$OH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.3, 170.2, 170.1, 170.0, 169.4, 169.2, 169.0, 148.1, 133.3, 101.1, 85.5, 75.9, 75.6, 72.6, 70.9, 70.8, 70.6, 69.1, 66.6, 61.6, 61.6, 60.8, 51.6, 21.9, 20.8, 20.7, 20.6, 20.6, 20.5, 20.1; HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{31}$H$_{43}$N$_3$O$_{18}$Na, 768.2434; found, 768.2426.

1-(Hepta-\textit{O}-acetyl-\textit{\-}\textbeta\textit{- lactosyl})-4-(1-hydroxyl-1-cyclohexyl)-1,2,3-triazole, compound 16 was obtained as a white solid, 83.2 mg in 70\% yield, mp 172.1-174.7 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 (s, 1H), 5.80 (d, $J = 8.6$ Hz, 1H), 5.42-5.34 (m, 3H), 5.13 (dd, $J = 7.9$, 10.6 Hz, 1H), 4.97 (dd, $J = 3.4$, 10.4 Hz, 1H), 4.53 (d, $J = 7.9$ Hz, 1H), 4.48 (d, $J = 11.6$ Hz, 1H), 4.17-4.07 (m, 3H),
3.98-3.88 (m, 3H), 2.15-1.85 (m, 21H), 1.96-1.91 (m, 2H), 1.93-1.91 (m, 1H), 1.89-1.86 (broad, 2H), 1.80-1.68 (m, 2H), 1.63-1.54 (m, 3H), 1.40-1.32 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.3, 170.2, 170.1, 170.0, 169.4, 169.1, 169.0, 156.2, 118.2, 101.1, 85.6, 75.9, 75.6, 72.6, 70.9, 70.9, 70.6, 69.5, 69.1, 66.6, 61.8, 60.8, 37.9, 25.3, 20.8, 20.7, 20.6, 20.5, 20.1; LC-MS m/z [M + H]$^+$ calcd for C$_{34}$H$_{48}$N$_3$O$_{18}$, 786.3; found 786.3.

1-(Hepta-<i>O</i>-acetyl-<i>β</i>-lactosyl)-4-(9-hydroxynonyl)-1,2,3-triazole, compound **17** was obtained as a white solid, 94.4 mg in 75% yield, mp 145.0-146.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.42 (s, 1H), 5.80-5.78 (m, 1H), 5.39-5.36 (m, 3H), 5.13 (dd, $J$ = 7.9, 10.5 Hz, 1H), 4.97 (dd, $J$ = 3.4, 10.4 Hz, 1H), 4.52 (d, $J$ = 7.8 Hz, 1H), 4.47 (dd, $J$ = 10.6, 12.0 Hz, 1H), 4.17-4.07 (m, 3H), 3.98-3.88 (m, 3H), 3.63 (t, $J$ = 6.6 Hz, 2H), 2.69 (t, $J$ = 7.5 Hz, 2H), 2.16-1.87 (m, 2H), 1.67-1.62 (m, 2H), 1.59-1.52 (m, 2H), 1.30 (broad, 11H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.3, 170.2, 170.1, 170.0, 169.4, 169.2, 169.0, 149.1, 118.7, 101.1, 85.4, 75.9, 75.7, 72.7, 70.9, 70.9, 70.5, 69.1, 66.0, 66.6, 63.0, 32.7, 29.4, 29.3, 29.2, 29.1, 21.1, 20.8; HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{37}$H$_{55}$N$_3$O$_{18}$Na, 852.3373; found, 852.3361.

1-(Hepta-<i>O</i>-acetyl-<i>β</i>-lactosyl)-4-(8-carboxyloctyl)-1,2,3-triazole, compound **18** was obtained as a white solid, 106.9 mg in 84% yield, mp 271.9-274.7 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.44 (s, 1H), 5.81-5.78 (m, 1H), 5.39-5.36 (m, 3H), 5.12 (dd, $J$ = 7.8, 10.4 Hz, 1H), 4.97 (dd, $J$ = 3.4, 10.6 Hz, 1H), 4.53 (d, $J$ = 7.9 Hz, 1H), 4.49 (dd, $J$ = 10.8, 12.1 Hz, 1H), 4.17-4.06 (m, 3H), 3.95-3.88 (m, 3H), 2.70 (t, $J$ = 7.5 Hz, 2H), 2.33 (t, $J$ = 7.4, 2H), 2.15-1.85 (m, 21H), 1.64-1.60 (m, 4H), 1.31 (broad, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 178.0, 170.4, 170.2, 170.1, 170.0, 169.4, 169.2, 169.0, 148.9, 118.9, 101.0, 85.5, 75.9, 75.6, 72.7, 70.9, 70.8, 70.5, 69.6, 61.8, 60.8, 33.8, 28.9, 28.9, 28.8,
25.4, 24.6, 20.7, 20.7, 20.6, 20.6, 20.4, 20.2; HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{37}$H$_{53}$N$_3$O$_{19}$Na, 866.3165; found, 866.3153.

1-(Hepta-\(O\)-acetyl-\(\beta\)-lactosyl)-4-phenyl-1,2,3-triazole, compound 19 was obtained a white solid, 98.5 mg in 85% yield as, mp 196.0-198.4 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.92 (s, 1H), 7.82-7.79 (m, 2H), 7.43-7.39 (m, 2H), 7.35-7.31 (m, 1H), 5.88 (d, $J$ = 9.0 Hz, 1H), 5.50-5.35 (m, 3H), 5.14 (dd, $J$ = 7.8, 10.4 Hz, 1H), 4.96 (dd, $J$ = 3.4, 10.5 Hz, 1H), 4.54 (d, $J$ = 7.9 Hz, 1H), 4.49 (dd, $J$ = 10.7, 12.0 Hz, 1H), 4.19-3.88 (m, 6H) 2.14-1.86 (m, 21H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.2, 170.1, 170.0, 170.0, 169.4, 169.1, 169.0, 148.2, 129.8, 128.7, 128.5, 125.8, 117.7, 101.0, 85.5, 75.9, 75.6, 72.6, 70.8, 70.8, 70.4, 69.0, 66.5, 61.7, 60.8, 20.7, 20.6, 20.5, 20.4, 20.1; LC-MS m/z: [M + Na]$^+$ calcd for C$_{34}$H$_{41}$N$_3$O$_{17}$Na, 786.2; found, 786.2.

1-(Hepta-\(O\)-acetyl-\(\beta\)-maltosyl)-4-butyl-1,2,3-triazole, compound 24 was obtained as a white solid, 39.6 mg in 70% yield, mp 123.0-125.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42 (s, 1H), 5.85 (d, $J$ = 9.3 Hz, 1H), 5.47-5.29 (m, 4H), 5.07 (dd, $J$ = 9.9, 10.0 Hz, 1H), 4.88 (dd, $J$ = 4.0, 10.5 Hz, 1H), 4.48 (dd, $J$ = 2.2, 12.4 Hz, 1H), 4.25 (dd, $J$ = 5.0, 12.5 Hz, 1H), 4.23 (dd, $J$ = 4.2, 12.2 Hz, 1H), 4.11 (dd, $J$ = 8.9, 9.9 Hz, 1H), 4.05 (dd, $J$ = 2.3, 12.5 Hz, 1H), 3.99-3.96 (m, 2H), 2.70 (t, $J$ = 7.8 Hz, 2H), 2.12–1.83 (m, 21H), 1.66-1.62 (m, 2H), 1.38-1.32 (m, 2H), 0.917 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.5, 170.4, 170.3, 169.8, 189.8, 169.4, 169.2, 149.1, 118.7, 95.9, 85.2,75.3, 75.2, 72.6, 70.9, 68.8, 68.0, 62.6, 61.5, 31.2, 25.2, 22.1, 20.8, 20.7, 20.6, 20.5, 20.1, 13.7; HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{32}$H$_{45}$N$_3$O$_{17}$Na, 766.2641; found, 766.2628.

1-(Hepta-\(O\)-acetyl-\(\beta\)-maltosyl)-4-hexyl-1,2,3-triazole, compound 25 was obtained as a white solid, 45.7 mg in 78% yield, mp 143.5-146.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42 (s, 1H), 5.85
(d, J = 9.3 Hz, 1H), 5.47-5.30 (m, 4H), 5.07 (dd, J = 9.7, 10.1 Hz, 1H), 4.88 (dd, J = 4.0, 10.5 Hz, 1H), 4.48 (dd, J = 2.4, 12.3 Hz, 1H), 4.25 (dd, J = 4.8, 9.4 Hz, 1H), 4.24 (dd, J = 4.1, 9.5 Hz, 1H), 4.11 (dd, J = 8.8, 9.9 Hz, 1H), 4.09 (dd, J = 2.3, 12.4 Hz, 1H), 4.00-3.95 (m, 2H), 2.70 (t, J = 7.9 Hz, 2H), 2.14–1.84 (m, 21H), 1.67-1.61 (m, 2H), 1.34-1.26 (m, 6H), 0.875 (t, J = 6.8 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 170.6, 170.5, 170.3, 169.9, 169.9, 169.4, 169.2, 149.1, 118.7, 95.9, 85.2, 75.3, 75.3, 69.3, 68.9, 68.0, 62.6, 61.5, 31.5, 29.1, 28.8, 25.6, 22.5, 20.8, 20.7, 20.7, 20.6, 20.1, 14.0; HRMS (ESI) m/z: [M + Na]+ calcd for C34H49N3O17Na, 794.2954; found, 794.2943.

1-(Hepta-O-acetyl-β-maltosyl)-4-octyl-1,2,3-triazole, compound 26 was obtained as a white solid, 42.7 mg in 71% yield, mp 153.7-156.0 °C. 1H NMR (400 MHz, CDCl3) δ 7.41 (s, 1H), 5.85 (d, J = 9.3 Hz, 1H), 5.45-5.32 (m, 4H), 5.07 (dd, J = 9.9, 10.3 Hz, 1H), 4.88 (dd, J = 4.1, 10.5 Hz, 1H), 4.48 (dd, J = 2.4, 12.5 Hz, 1H), 4.25 (dd, J = 4.9, 12.3 Hz, 1H), 4.23 (dd, J = 4.1, 12.4 Hz, 1H), 4.11 (dd, J = 8.8, 9.7 Hz, 1H), 4.06 (dd, J = 2.2, 12.5 Hz, 1H), 3.99-3.96 (m, 2H), 2.69 (t, J = 7.8 Hz, 2H), 2.12–1.83 (m, 21H), 1.67-1.60 (m, 2H), 1.31-1.26 (m, 10H), 0.870 (t, J = 7.0 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 170.5, 170.4, 170.3, 169.8, 169.8, 169.4, 169.2, 149.1, 118.7, 95.9, 85.1, 75.3, 75.2, 72.6, 70.9, 70.0, 69.2, 62.6, 61.5, 31.8, 29.2, 29.1, 25.6, 22.6, 20.8, 20.7, 20.6, 20.5, 20.1, 14.0; HRMS (ESI) m/z: [M + H]+ calcd for C36H54N3O17, 800.3448; found, 800.3447.

1-(Hepta-O-acetyl-β-maltosyl)-4-(4-chlorobutyl)-1,2,3-triazole, compound 27 was obtained as a white solid, 47.5 mg in 81% yield, mp 176.7-278.4 °C. 1H NMR (400 MHz, CDCl3) δ 7.45 (s, 1H), 5.85 (d, J = 9.3 Hz, 1H), 5.47-5.28 (m, 4H), 5.07 (dd, J = 9.8, 10.5 Hz, 1H), 4.88 (dd, J = 4.00, 10.6 Hz, 1H), 4.48 (dd, J = 2.3, 12.4 Hz, 1H), 4.27 (dd, J = 4.8, 12.1 Hz, 1H), 4.25 (dd, J = 4.1, 12.2 Hz, 1H), 4.11 (dd, J = 8.9, 9.7 Hz, 1H), 4.07 (dd, J = 2.1, 12.5 Hz, 1H), 3.99-3.96 (m, 2H),
3.54 (t, \(J = 6.0\) Hz, 2H), 2.75 (t, \(J = 6.6\) Hz, 2H), 2.12–1.84 (m, 21H), 1.83-1.81 (m, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 170.5, 170.4, 170.3, 169.8, 169.4, 169.2, 148.2, 118.9, 95.9, 85.2, 75.4, 75.1, 72.5, 70.9, 70.0, 69.2, 68.8, 68.0, 62.5, 61.5, 44.6, 31.8, 26.3, 24.8, 20.8, 20.7, 20.6, 20.5, 20.1; HRMS (ESI) m/z: [M + Na]\(^+\) calcd for C\(_{32}\)H\(_{44}\)ClN\(_3\)O\(_7\)Na, 800.2251; found, 800.2237.

1-(Hepta-O-acetyl-\(\beta\)-maltosyl)-4-(hydroxymethyl)-1,2,3-triazole, compound 28 was obtained as a white solid, 44.1 mg in 81% yield, mp 215.0-217.9 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.65 (s, 1H), 5.89 (d, \(J = 9.3\) Hz, 1H), 5.48-5.31 (m, 4H), 5.06 (dd, \(J = 9.8, 10.4\) Hz, 1H), 4.85 (dd, \(J = 4.0, 10.5\) Hz, 1H), 4.76 (s, 1H), 4.48 (dd, \(J = 2.4, 12.3\) Hz, 1H), 4.29 (dd, \(J = 4.8, 12.4\) Hz, 1H), 4.26 (dd, \(J = 4.0, 12.2\) Hz, 1H), 4.17 (dd, \(J = 8.6, 9.8\) Hz, 1H), 4.10 (dd, \(J = 2.3, 12.5\) Hz, 1H), 4.00-3.95 (m, 2H), 2.11–1.84 (m, 21H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 170.5, 170.5, 170.3, 169.9, 169.9, 169.4, 169.3, 95.9, 85.3, 75.4, 75.1, 72.4, 71.0, 70.0, 68.8, 68.0, 62.5, 61.5, 56.6, 20.8, 20.7, 20.6, 20.6, 20.5, 20.2; HRMS (ESI) m/z: [M + Na]\(^+\) calcd for C\(_{29}\)H\(_{39}\)N\(_3\)O\(_{18}\)Na, 740.2121; found, 740.2114.

11-(Hepta-O-acetyl-\(\beta\)-maltosyl)-4-(3-hydroxylpropyl)-1,2,3-triazole, compound 29 was obtained as a white solid, 46.8 mg in 83% yield, mp 183.9-185.4 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.48 (s, 1H), 5.87 (d, \(J = 9.4\) Hz, 1H, H-1), 5.48-5.27 (m, 4H, H-3', H-1', H-2, H-3), 5.07 (t, \(J = 9.8\) Hz, 1H, H-4'), 4.90 (dd, \(J = 4.0, 10.5\) Hz 1H, H-2'), 4.51 (dd, \(J = 2.4, J = 12.4\) Hz, 1H, H-6a), 4.29 (dd, \(J = 4.9, J = 10.8\) Hz, 1H, H-6b), 4.26 (dd, \(J = 4.9, 10.0\) Hz, 1H, H-6a'), 4.16-4.06 (m, 2H, H-6b', H-4), 3.99-3.95 (m, 2H, H-5, H-5'), 3.67 (t, \(J = 6.1\) Hz, 2H, CH\(_2\)-OH), 2.83 (t, \(J = 7.3\) Hz, 2H, CH\(_2\) (CH\(_2\))\(_2\)-OH), 2.12–1.84 (m, 21H, (OAc)\(_7\)), 1.95-1.91 (m, 2H, CH\(_2\)CH\(_2\)OH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 170.6, 170.4, 170.3, 169.9, 169.8, 169.4, 169.3, 148.1, 119.2, 95.9, 85.3, 75.4,
HRMS (ESI) m/z: [M + Na]\(^+\) calcd for C\(_{31}\)H\(_{43}\)N\(_3\)O\(_{18}\)Na, 768.2434; found, 768.2420.

1-(Hepta-O-acetyl-\(\beta\)-maltosyl)-4-(1-hydroxyl-1-cyclohexyl)-1,2,3-triazole, compound **30** was obtained as a white solid, 47.6 mg in 80\% yield, mp 189.7-190.2 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.61 (s, 1H), 5.85 (d, \(J = 9.2\) Hz, 1H), 5.47-5.29 (m, 4H), 5.06 (dd, \(J = 9.5, 10.2\) Hz, 1H), 4.87 (dd, \(J = 4.1, 10.6\) Hz, 1H), 4.48 (dd, \(J = 2.4, 12.5\) Hz, 1H), 4.26 (dd, \(J = 4.6, 12.8\) Hz, 1H), 4.24 (dd, \(J = 4.1, 12.4\) Hz, 1H), 4.11 (dd, \(J = 8.7, 9.9\) Hz, 1H), 4.09 (dd, \(J = 2.3, 12.5\) Hz, 1H), 3.99-3.95 (m, 2H), 2.12-1.83 (m, 21H), 1.96-1.31 (m, 10H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 170.5, 170.4, 170.3, 169.8, 169.3, 169.1, 156.1, 118.1, 95.5, 85.2, 75.3, 75.0, 72.5, 71.0, 67.9, 62.5, 61.4, 37.9, 25.2, 21.8, 20.7, 20.7, 20.6, 20.5, 20.1; LC-MS m/z [M + H]\(^+\) calcd for C\(_{34}\)H\(_{48}\)N\(_3\)O\(_{18}\), 786.3; found 786.3.

1-(Hepta-O-acetyl-\(\beta\)-maltosyl)-4-(9-hydroxylnonyl)-1,2,3-triazole, compound **31** was obtained as a white solid, 48.5 mg in 87\% yield, mp 156.5-158.04 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.42 (s, 1H), 5.85 (d, \(J = 9.3\) Hz, 1H), 5.47-5.30 (m, 4H), 5.07 (dd, \(J = 9.8, 10.0\) Hz, 1H), 4.89 (dd, \(J = 4.0, 10.6\) Hz, 1H), 4.48 (dd, \(J = 2.4, 12.2\) Hz, 1H), 4.26 (dd, \(J = 4.9, 10.7\) Hz, 1H), 4.24 (dd, \(J = 3.9, 10.7\) Hz, 1H), 4.11 (dd, \(J = 9.0, 9.6\) Hz, 1H), 4.06 (dd, \(J = 2.2, 12.7\) Hz, 1H), 4.00-3.96 (m, 2H), 3.63 (t, \(J = 6.6\) Hz, 2H), 2.69 (t, \(J = 7.6\) Hz, 2H), 2.12-1.84 (m, 21H), 1.67-1.30 (m, 14H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 170.5, 170.4, 170.3, 169.8, 169.3, 169.2, 149.0, 118.7, 95.9, 85.1, 75.3, 75.2, 72.5, 70.9, 70.0, 69.2, 68.7, 67.9, 63.0, 62.5, 61.4, 32.7, 29.3, 29.2, 29.1, 29.0, 29.0, 25.6, 25.4, 20.7, 20.7, 20.6, 20.5, 20.1; HRMS (ESI) m/z: [M + H]\(^+\) calcd for C\(_{37}\)H\(_{56}\)N\(_3\)O\(_{18}\), 830.3553; found, 830.3550.
1-(Hepta-\(O\)-acetyl-\(\beta\)-maltosyl)-4-(8-carboxyloctyl)-1,2,3-triazole, compound 32 was obtained as a white solid, 51.6 mg in 81% yield, mp 151.5-154.5 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.42 (s, 1H), 5.85 (d, \(J = 9.3\) Hz, 1H), 5.47-5.29 (m, 4H), 5.06 (dd, \(J = 9.8, 10.0\) Hz, 1H), 4.87 (dd, \(J = 3.9, 10.5\) Hz, 1H), 4.49 (dd, \(J = 2.4, 12.4\) Hz, 1H), 4.26 (dd, \(J = 5.0, 11.6\) Hz, 1H), 4.23 (dd, \(J = 3.8, 12.0\) Hz, 1H), 4.13 (dd, \(J = 8.9, 9.5\) Hz, 1H), 4.07 (dd, \(J = 2.1, 12.4\) Hz, 1H), 3.99-3.96 (m, 2H), 2.69 (t, \(J = 7.7\) Hz, 2H), 2.33 (t, \(J = 7.4\) Hz, 2H), 2.11–1.79 (m, 21H), 1.64-1.60 (m, 4H), 1.31 (broad S, 8H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 178.3, 170.6, 170.5, 170.3, 169.9, 169.9, 169.4, 169.3, 149.0, 118.8, 95.9, 85.2, 75.3, 75.2, 72.6, 70.9, 70.0, 69.2, 68.7, 68.0, 62.6, 61.5, 33.8, 29.0, 28.9, 28.9, 25.5, 24.6, 20.7, 20.7, 20.6, 20.5, 20.1; HRMS (ESI) m/z: [M + Na]\(^+\) calcd for C\(_{37}\)H\(_{53}\)N\(_3\)O\(_{19}\)Na, 866.3165; found, 866.3151.

1-(Hepta-\(O\)-acetyl-\(\beta\)-maltosyl)-4-phenyl-1,2,3-triazole, compound 33 was obtained as a white solid, 47.0 mg in 82% yield, mp 210.0-211.4 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.92 (s, 1H), 7.84-7.81 (m, 2H), 7.45-7.41 (m, 2H), 7.37-7.33 (m, 1H), 5.96 (d, \(J = 9.1\) Hz, 1H), 5.51-5.36 (m, 4H), 5.10 (dd, \(J = 9.8, 10.0\) Hz, 1H), 4.92 (dd, \(J = 4.0, 10.5\) Hz, 1H), 4.52 (dd, \(J = 2.4, 12.3\) Hz, 1H), 4.29 (dd, \(J = 4.8, 12.4\) Hz, 1H), 4.04-3.97 (m, 2H), 2.13–1.86 (m, 21H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 170.6, 170.4, 170.3, 169.9, 169.8, 169.4, 169.3, 148.4, 129.9, 128. 9, 128.6, 125.9, 117.7, 95.9, 85.3, 75.4, 72.5, 70.9, 69.2, 68.8, 67.9, 62.5, 61.5, 20.8, 20.7, 20.6, 20.5, 20.2; LC-MS m/z: [M + Na]\(^+\) calcd for C\(_{34}\)H\(_{41}\)N\(_3\)O\(_{17}\)Na, 786.2; found, 786.2.

1-(Hepta-\(O\)-acetyl-\(\beta\)-maltosyl)-4-(3-phenylpropyl)-1,2,3-triazole, compound 34 was obtained as a white solid, 48.8 mg in 80% yield, mp 178.0-181.0 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.43 (s, 1H.), 7.30-7.25 (m, 2H), 7.19-7.16 (m, 3H), 5.86 (d, \(J = 9.3\) Hz, 1H), 5.47-5.28 (m, 4H), 5.07 (dd,
$J = 9.8 \text{ Hz}, 10.0 \text{ Hz}, 1H)$, 4.88 (dd, $J = 4.0, 10.5 \text{ Hz}, 1H$), 4.48 (dd, $J = 2.4, 12.3 \text{ Hz}, 1H$), 4.29 (dd, $J = 4.8 \text{ Hz}, J = 12.4 \text{ Hz}, 1H$), 4.26 (dd, $J = 4.0 \text{ Hz}, J = 12.2 \text{ Hz}, 1H$), 4.17 (dd, $J = 8.6, 9.8 \text{ Hz}, 1H$), 4.1 (dd, $J = 2.3, 12.5 \text{ Hz}, 1H$), 4.03-3.92 (m, 2H), 2.74 (t, $J = 7.6 \text{ Hz}, 2H$), 2.65 (t, $J = 7.8 \text{ Hz}, 2H$), 2.0 (m, 2H) 2.12–1.83 (m, 21H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.5, 170.5, 170.3, 169.9, 169.9, 169.4, 169.3, 148.6, 141.7, 128.5, 128.4, 125.9, 118.9, 95.9, 85.3, 75.4, 75.1, 72.4, 71.0, 70.0, 68.8, 68.0, 62.5, 61.5, 35.2, 30.7, 25.1, 20.8, 20.7, 20.6, 20.5, 20.2; HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{37}$H$_{47}$N$_3$O$_{17}$Na, 828.2798; found, 828.2784.

Compound 35 was obtained as a white solid, 85.0 mg in 79% yield, mp decomposed on heating to form a brown solid at 180.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45 (s, 1H), 5.84 (d, $J = 9.2 \text{ Hz}, 1H$), 5.46-5.29 (m, 4H), 5.06 (dd, $J = 9.8, 10.0 \text{ Hz}, 1H$), 4.87 (dd, $J = 3.9, 10.4 \text{ Hz}, 1H$), 4.47 (dd, $J = 2.2, 12.6 \text{ Hz}, 1H$), 4.25 (dd, $J = 4.5, 12.4 \text{ Hz}, 1H$), 4.22 (dd, $J = 3.7, 12.6 \text{ Hz}, 1H$), 4.12 (dd, $J = 8.9, 9.5 \text{ Hz}, 1H$), 4.07 (dd, $J = 2.2, 12.5 \text{ Hz}, 1H$), 3.98-3.94 (m, 2H), 2.73 (broad, 2H), 2.11–1.82 (m, 21H), 1.72 (broad, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.5, 170.4, 170.3, 169.8, 169.3, 169.2, 148.5, 119.0, 95.9, 85.2, 75.3, 75.2, 72.5, 70.9, 70.6, 69.2, 68.7, 67.9, 62.5, 61.4, 28.5, 25.2, 20.8, 20.7, 20.6, 20.5, 20.1; HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{60}$H$_{80}$N$_6$O$_{34}$Na, 1451.4582; found, 1451.4582.

Compound 36 was obtained as a white solid, 84.8 mg in 78% yield, mp 205.4-207.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.43 (s, 1H), 5.85 (d, $J = 9.3 \text{ Hz}, 1H$), 5.47-5.29 (m, 4H), 5.06 (dd, $J = 9.8, 9.9 \text{ Hz}, 1H$), 4.88 (dd, $J = 4.0, 10.5 \text{ Hz}, 1H$), 4.48 (dd, $J = 2.3, 12.3 \text{ Hz}, 1H$), 4.24 (dd, $J = 4.5, 12.4 \text{ Hz}, 1H$), 4.23 (dd, $J = 4.0, 12.4 \text{ Hz}, 1H$), 4.11 (dd, $J = 8.9, 9.8 \text{ Hz}, 1H$), 4.07 (dd, $J = 2.2, 12.4 \text{ Hz}, 1H$), 4.00-3.95 (m, 2H), 2.70 (t, $J = 7.7 \text{ Hz}, 2H$), 2.12–1.83 (m, 21H), 1.73-1.66 (m, 2H), 1.40-1.37 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.6, 170.5, 170.3, 169.9, 169.4, 169.2, 148.8,
118.8, 95.9, 85.2, 75.3, 75.4, 72.2, 72.6, 70.9, 70.0, 69.3, 68.8, 68.0, 62.56, 61.5, 28.8, 28.5, 25.4, 20.8, 20.8, 20.7, 20.6, 20.1; HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{61}$H$_{82}$N$_6$O$_{34}$Na, 1465.4764; found, 1465.4740.
CHAPTER 3

SYNTHESIS AND CHARACTERIZATION OF UV LIGHT AND pH RESPONSIVE D-GLUCOSAMINE BASED LOW MOLECULAR WEIGHT GELATORS

3.1 INTRODUCTION

The Nobel Prize for Chemistry awarded to three scientists, Pedersen, Cram, and Lehn for their work in the area of supramolecular chemistry in 1987 helped announce the significance of supramolecular chemistry in the science community. From the late nineteenth century, great interest have been paid to the field of supramolecular chemistry.\textsuperscript{145} Supramolecular gel is an interesting soft material that has gained extensive attention for applications in the field of biology, materials, environment, and biomedicine science.\textsuperscript{18,146-148} Low molecular weight gelators (LMWGs) are small molecules that are able to immobilize solvents and form supramolecular or physical gels.\textsuperscript{149} The formation of supramolecular gels is based on non-covalent intermolecular forces such as hydrogen bonding, $\pi-\pi$ interactions, hydrophobic forces and van der Waals interactions forming one-dimensional structure such as fibre. The interaction of the individual fibre leads to the formation of a gel.\textsuperscript{150,151}

Compounds of biological origin and natural products such as amino acids, peptides, carbohydrates, nucleic acids, cholesterol have been reported to be effective gelators and have been found to have numerous applications such as sensors,\textsuperscript{152} for the preparation of tissue engineering scaffolds,\textsuperscript{153} as catalyst,\textsuperscript{154} drug release,\textsuperscript{142} protein purification using supramolecular gel electrophoresis\textsuperscript{30} and in waste cleaning in marine oil spill\textsuperscript{114}. Among the various natural products, carbohydrates are especially promising because they are
renewable resources and have large structural diversity. For the past decade we have been working on the design and synthesis of carbohydrate based LMWGs and have gained a good insight on how to functionalize monosaccharide derivatives as LMWGs.\textsuperscript{155,156}

Stimuli-responsive supramolecular gels are able to respond to a variety of chemical stimuli (pH change, ionic, etc.) and physical stimuli (light, sonication, mechanical force, etc.) and often exhibit color change, isomerization, gel-to-sol transition, sol-to-gel transition, gel-to-gel transition and change in morphology due to the reversible non-covalent interactions of the gels.\textsuperscript{7,157-160} These properties make the gel useful as smart materials. The use of light as an external stimulus has found applications in biomedical application because of its ability to spatially target a specific region of the gel leading to patterned gel surfaces.\textsuperscript{21,161-163}

Among the reported light-responsive groups, 2-nitrobenzyl derivatives (\textit{o-NB}) have gained wide acceptance and a myriad number of light-responsive biologically active compounds that have been prepared belong to the \textit{o-NB} series. This is because of their versatile modification and well-known photolysis mechanism which is based on the photoisomerization of an \textit{o}-nitrobenzyl alcohol derivative into the corresponding \textit{o}-nitrosobenzaldehyde upon irradiation with UV light.\textsuperscript{162,164-168} The design of carbohydrate based gels that are responsive to UV light irradiation is of interest to us as they have potential application as drug delivery. In this chapter, we report the synthesis and systematic characterization of a series of photo-responsive sugar-based gelators. Their self-assembling properties in water, organic solvents and aqueous solutions were also studied. The synthesis was done efficiently and we found several molecules with excellent gelation abilities for organic solvents.
3.2 RESULTS AND DISCUSSION

SYNTHESIS OF SUGAR HEADGROUP

The sugar headgroup, 4 used for the synthesis of the sugar-based light responsive gelator was synthesized as shown in Scheme 14: Methoxy-4,6-O-benzylidene-2-deoxy-2-amino-α-D-glucopyranoside (4) was synthesized according to previous report with slight modification.  

$\text{N\text{-Acetyl-D-glucosamine 1 (2.0 g, 9.04 mmol) was dissolved in 10 mL methanol in a 100 mL round bottom flask. Acid resin (2.0 g) was rinsed with methanol and then added into the reaction mixture. The reaction was refluxed for 24 h. }^{1}$H NMR shows complete conversion of the sugar starting material. The crude product was allowed to cool and then filtered. The resin was washed with methanol and the combined crude product was concentrated under reduced pressure to obtain an off-white solid as product, 1.89 g, 89% yield. Methyl 2-acetamido-2-deoxy-α-D-glucopyranoside, 2 (1.89 g, 8.03 mmol, 1 equiv) was dissolved in 10 mL DMF. Benzaldehyde dimethyl acetal (1.45 mL, 9.64 mmol, 1.2 equiv) and p-toluenesulfonic acid (0.153 g, 0.803 mmol, 0.1 equiv) were added and the reaction mixture was heated at 70 °C for 12 h. Reaction was stopped and the methanol by-product was removed under reduced pressure. Then sodium bicarbonate (135 mg) was added and the mixture was stirred for 20 minutes. The salt was filtered, DMF was removed under reduced pressure. The crude mixture was purified by recrystallization in ethanol to get the desired product, compound 3 as a white solid, 2.08 g, 80%. Compound 3 (2.00g) was then dissolved in 20 mL of 3N NaOH in ethanol. Reaction was refluxed for 36 h. Reaction mixture was concentrated under reduced pressure and then diluted with DCM (30 mL x 2) and washed with water (2x20 mL). The organic phase was dried over anhydrous sodium sulphate and the pure product, compound 4 was obtained as a yellow solid, 1.6 g, 92% yield.
SYNTHESIS OF SUGAR-BASED LIGHT AND pH RESPONSIVE GELATORS

The derivatives of 2-nitrobenzyl alcohol were synthesized as outlined in **Scheme 15**. The 2-nitrobenzyl acids derivatives 6-10 were converted to the corresponding acid chlorides by treating them with oxaly chloride in dichloromethane and one drop of DMF at 0 °C. Reaction of the sugar headgroup 4 with derivatives of 2-nitrobenzyl acid chlorides afforded the desired multi responsive sugar-based compounds 12-16 as shown in **Scheme 16**.

Another class of sugar-based photo-responsive based gelators that links the sugar head group to the 2-nitrobenzyl derivatives via an ester group was also synthesized. The headgroup, 4 was converted to the bromide derivative as shown in **Scheme 17**. Finally, a new class of sugar based multi responsive compounds 18-23 were synthesized by displacement of the bromide with a carboxylic acid functional group as shown in **Scheme 18**. All the compounds were purified using column chromatography using a solvent mixture of MeOH/DCM.
The gelation abilities of these compounds were evaluated in a series of solvent as shown in Table 6. We are more interested in the gelation result in water and in aqueous solutions. This is because of their potential applications in drug delivery and biological studies. From Table 6, for the amide series 12-16, it was observed that most of the 2-nitrobenzyl based compounds were good gelators in aqueous solvents. None of the compounds were good gelators in hexane while only compound 13 formed a hydrogel at a higher concentration. Compound 15 was not a good gelator as it did not form a stable effective gel in any of the solvents tested. All of the compounds tested formed gel in aqueous solution except compound 15. Compounds 13 and 16 were the best performing compounds as they both form gels at 0.22 wt % in a DMSO:H2O (1:2) mixture.

The gelation abilities of compounds 18-23 were also evaluated in a series of solvent as shown in Table 6. From Table 6, it was observed that most of the 2-nitrobenzyl based compounds were good gelators in aqueous solvents. None of the compounds were good gelators in hexane while only compound 18 formed a hydrogel at a higher concentration. Compound 21 and 22 formed gel in toluene while all the compounds formed gel in isopropanol except compound 20. Ethanol was a good solvent for gelation for all the compounds tested except for compound 19 where a precipitate was formed. DMSO:H2O was a good solvent mixture for gelation for all the compounds except for compound 21 where a precipitate was formed in a DMSO:H2O (1:2). Compounds 22 and 23 were the best performing compounds. Figure 53 shows pictures of some of the gels.
**Scheme 15.** Synthesis of acid starting materials.

5a: $R = H$
5b: $R = \text{OCH}_3$

7a: $R = H$
7b: $R = \text{OCH}_3$

9a: $R = H$
9b: $R = \text{OCH}_3$

$\text{DMAP, Chloroform, reflux, 24 h}$

10a: $R = H$, 76%
10b: $R = \text{OCH}_3$, 89%

6a: $R = H$, 84%
6b: $R = \text{OCH}_3$, 89%

8a: $R = H$, 91%
8b: $R = \text{OCH}_3$, 95%
Scheme 17. Synthesis of compound 17.

Figure 53. The photos of the gels formed by some of the gelators. A: compound 12 in DMSO:H$_2$O (v 1:2) at 2.8 mg/mL; B: compound 16 in DMSO:H$_2$O (v 1:2) at 2.2 mg/mL; C: compound 18 in EtOH:H$_2$O (v 1:2) 5.0 mg/mL; D: compound 23 in DMSO:H$_2$O (v 1:2) at 4.0 mg/mL.
Scheme 18. Synthesis of a different class of sugar based light and pH responsive compounds 18-23.
Table 6. Gelation test results for the series of light and pH responsive compounds.

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<td>G 4.0</td>
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<td>I</td>
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G, gel at room temperature; the numbers are the corresponding minimum gelation concentrations (MGCs) in mg/mL. I, insoluble. P, precipitate. S, soluble at ∼20 mg/mL. All the compounds were insoluble in hexane.

The rheology properties of some of the gels formed by the amide linked responsive compounds were characterized and are shown in Figure 54. For all the compounds, the storage modulus $G'$ was greater than the loss modulus $G''$ at all tested frequencies. This is an indication of the gel’s elastic properties. The storage modulus for compound 12 was about 11,000 Pa, which is the strongest among the compounds tested.
Figure 54. Rheology properties of some of the gels formed at 5% strain. Compound 12, 2.8 mg/mL in DMSO:H$_2$O (v/v = 1:2); compound 13, 2.2 mg/mL in DMSO:H$_2$O (v/v = 1:2); compound 14, 4.0 mg/mL in EtOH:H$_2$O (v/v = 1:1) and compound 16, 2.2 mg/mL in DMSO:H$_2$O (v/v = 1:2).

The optical micrographs of the several tested multi-responsive sugar lipids in this study were also studied. Very interesting and unique morphologies were formed in the gel phase when observed under an optical microscope as shown in Figure 55. The gel formed by compound 16 in EtOH:H$_2$O (v 1:2) at 3.3 mg/mL had very unique morphology as they form planner sheets with some fibrous structures (Fig. 55A). In contrast, the gel formed by compound 12 in EtOH:H$_2$O (v 1:1) at 10.0 mg/mL exhibited long and dense fibrous assemblies, with length scale at several hundreds of
microns (Fig. 55B and Fig. 55C). Figures 55D and 55E showed the morphology of gel formed by compound 13 in DMSO:H₂O (v 1:1) at 6.7 mg/mL. This gel formed shorter fibers while Figure 55F is also formed by compound 13 in EtOH:H₂O (v 1:1) at 5 mg/mL. This gel formed long and dense fibrous network. The optical micrograph of the gel formed by gelator 19 was also studied. Very interesting and unique morphologies were formed in the gel phase. The gel formed by compound 19 in EtOH: H₂O (v 1:2), 4.0 mg/mL exhibited long and thin fibrous assemblies.

In order to understand the self-assembling process and the effect of hydrogen bond in compound 12 we performed ¹H-NMR studies at different temperatures using CDCl₃. As shown in Figure 56, the NH peak in compound 12 shifted upfield from 5.98 ppm to 5.94 ppm upon increasing the temperature from 30 °C to 55 °C. This upfield shift shows a reduction in the intermolecular hydrogen bonding between the compounds as temperature increases. The anomeric proton also shifted slightly from 4.69 ppm to 4.70 ppm. Similarly, one of the aromatic protons of the 2-nitrobenzyl protons also shifted to a lower frequency upon increasing the temperature. The chemical shift went from 8.09 ppm to 8.07 ppm.

In order to understand the self-assembling process and the effect of hydrogen bonding in compound 14, we also performed ¹H-NMR studies at different temperatures using CDCl₃. This is shown in Figure 57. The NH peak in compound 14 as shown in Figure 57 shifted upfield from 7.04 ppm to 6.92 ppm upon increasing the temperature from 30 °C to 55 °C. This upfield shift shows a reduction in the intermolecular hydrogen bonding between the compounds as temperature increases. Similarly, one of the aromatic protons of the 2-nitrobenzyl protons also shifted to a lower frequency upon increasing the temperature (Figure 58).
Figure 55. Optical micrographs of the gels formed by the different light-responsive gelators. (a) compound 16 in EtOH:H₂O (v 1:2) at 3.3 mg/mL at 20 µm; (b, c) compound 12 in EtOH:H₂O (v 1:1) at 10.0 mg/mL at 10 µm; (d, e, f) compound 13 in EtOH:H₂O (v 1:1) at 5.0 mg/mL at 10 µm; (g, h) compound 19 in EtOH:H₂O (v 1:2), at 4.0 mg/mL at 20 µm.
The anomeric proton also shifted slightly from 4.73 ppm to 4.74 ppm (Figure 59). Also, the acidic proton between the two carbonyl groups also shifted slightly from 3.49 to 3.47 ppm upon increasing the temperature (Figure 59). Based on this study, it can be deduced that the chemical shift changes at higher temperatures are due to the change of the hydrogen bonding interactions of the amide group and the π-π stacking of the phenyl region. This indicated that π-π interactions and hydrogen bonding are important for the molecule self-assembly and may affect the gelation behavior.

For compound 16, the amide bond NH peak also shifted to a lower frequency at higher temperatures. The NH peak shifted upfield from 5.93 at 30 °C to 5.87 at 55 °C (Figure 60). This is also due to a reduction in the intermolecular hydrogen bonding between the compounds as temperature increases. Just like in compound 12 the anomeric proton also shifted slightly from 4.71 ppm to 4.72 ppm. Slight shifts in peaks were also observed for the methoxy peak and for the CH₂ in the benzyl compound. The aromatic peaks also shifted slightly (Figure 61).
Figure 56. $^1$H-NMR spectra at variable temperature of compound 12 from 30 °C to 55 °C in CDCl$_3$. 
**Figure 57.** $^1$H-NMR spectra at variable temperature of compound 14 from 30 °C to 55 °C in CDCl$_3$. 
Figure 58. $^1$H-NMR spectra at variable temperature of compound 14 from 30 °C to 55 °C in CDCl$_3$ for the expansion of the aromatic region.
Figure 59. $^1$H-NMR spectra at variable temperature of compound 14 from 30 °C to 55 °C in CDCl$_3$ full range.
Figure 60. $^1$H-NMR spectra at variable temperature of compound 16 from 30 °C to 55 °C in CDCl$_3$. 
Figure 61. $^1$H-NMR spectra at variable temperature of compound 16 from 30 °C to 55 °C in CDCl$_3$ for full range.

The potential application of UV light responsive carbohydrate based gelators in drug delivery and biological studies meant that we are especially interested in an effective gelator for water or aqueous solution with minimum amount of organic solvent. We are especially interested in finding effective LMWGs for water or aqueous solutions because of their potential applications in drug delivery and biological studies. Unfortunately, most of the gels formed were not effective
hydrogels. Thus, a study on the formation of gelators in aqueous solution at a high concentration of water was carried out to determine the minimum concentration of the gelators. The aqueous solution used was a mixture of water and dimethyl sulfoxide (DMSO). DMSO was chosen because it is a polar organic solvent that is miscible with water. DMSO is a very good solvent for solubilizing many organic molecules. DMSO still has some application in veterinary medicine and as a common industrial solvent.

Following the gelation test results in Table 6, a series of compounds were chosen for this study for the formation of effective gelators in aqueous solution with minimum amount of DMSO. From the compounds tested, four compounds 13, 14, 16 and 18 (Figure 62) formed effective gelators as shown in Table 7. From the gelation result in Table 7, the studies on the potential application of the UV light and pH responsive carbohydrate based gelators in drug delivery and biological studies can be carried out.

**The gelation test analysis at minimum DMSO concentration**

In a 1 mL dram vial, 2 mg of compound 13 was dissolved in 0.05 mL of DMSO before the addition of 0.05 mL of water. The mixture formed an unstable gel, thus heating and subsequent cooling of the gel to room temperature was required. At this point, the vial was inverted to observe whether a stable gel was formed. If a stable gel is formed, then serial dilution of the gel was performed by adding 0.1 mL of water until the minimum gelation concentration was determined. A similar analysis was carried out for compounds 14, 16 and 18. Only compounds 16 and 18 formed a spontaneous gel at G 20.0, DMSO:H₂O (1:1) The ratio of DMSO and water in volume is calculated as shown in Table 7
The effects of UV light on the gelators were analyzed. A solution of compound 13, 2 mg in 2.5 mL ethanol was irradiated with UV light at 365 nm for 4 h. The exposure of the gelator to UV light caused the compound to decompose as the solution changed from colorless to light yellow solution (Figure 63). TLC and LCMS analysis also confirms the cleavage of the 2-nitro benzyl derivative as to afford the acid derivative. LCMS spectrum showing the acid derivative is shown in Figure 64. Moreover, when a solution of compound 14, 2 mg in 2.5 mL ethanol was irradiated with UV light for 4 h, the exposure of the gelator to UV light also caused the compound to decompose. TLC and LCMS analysis also confirms the cleavage of the 2-nitro benzyl derivative. LCMS spectrum showing the acid derivative is shown in Figure 65.

Following these results and in addition to literature report that shows that 4,5-dimethoxy derivatives of 2-nitrobenzyl alcohol absorbs at longer wavelength than 2-nitrobenzyl alcohol, we anticipate that the light responsive gelator, 14 may have application for controlled drug release.
Table 7. Gelation test table at minimum DMSO concentration. 2 mg of gelator dissolved in an aqueous solution of DMSO:H₂O in various ratio. MGC is minimum gelation concentration.

<table>
<thead>
<tr>
<th>Cpd No.</th>
<th>DMSO:H₂O initial solvent</th>
<th>0.1 mL H₂O</th>
<th>0.1 mL H₂O</th>
<th>0.1 mL H₂O</th>
<th>0.1 mL H₂O</th>
<th>Ratio (DMSO: H₂O)</th>
<th>% of DMSO</th>
<th>MGC</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>0.1 mL</td>
<td>G</td>
<td>G</td>
<td>G</td>
<td>x</td>
<td>0.05:0.45</td>
<td>10%</td>
<td>G 4.0</td>
</tr>
<tr>
<td>14</td>
<td>0.1 mL</td>
<td>G</td>
<td>G</td>
<td>G</td>
<td>x</td>
<td>0.05:0.35</td>
<td>12.5%</td>
<td>G 5.0</td>
</tr>
<tr>
<td>16</td>
<td>0.1 mL</td>
<td>G</td>
<td>G</td>
<td>0.05 mL</td>
<td>x</td>
<td>0.05:0.40</td>
<td>11.1%</td>
<td>G 4.4</td>
</tr>
<tr>
<td>18</td>
<td>0.1 mL</td>
<td>G</td>
<td>G</td>
<td>x</td>
<td></td>
<td>0.05:0.25</td>
<td>16.7%</td>
<td>G 6.7</td>
</tr>
</tbody>
</table>

Figure 62. Structure of compounds 13, 14, 16 and 18.
(A) Effect of UV light on compounds 13 and (B) 14 in ethanol. A solution of compound 13 and compound 14, 2 mg in 2.5 mL ethanol respectively was irradiated with UV light at 365 nm for 4 h.

The effect of pH on the four gelators was also studied. All the gels were observed to be stable at both pH 7 and pH 10 after 24 h. While the gelators formed by compounds 16 and 13 were stable in pH 12 after 24 h, the gelators formed by compounds 14 and 18 dissolved in pH 12 after 24 h. The dissolution of the gel formed by compound 14 and 18 in pH 12 was because the compounds have an acidic proton between the carbonyl functional groups. The basic solution (pH 12) was strong enough to deprotonate the compounds. All the gels were observed to dissolve at pH 14 (Table 8, Figure 66). The gel formed by compound 13 dissolved after 2 h while for compound 14, the gel floated after 1 hour before dissolving completely after 3 h in pH 14. For compound 16, the gel dissolved after 3 h while the gel formed by compound 18 floated after an hour before dissolving after 2 h.
Figure 64. (A) LCMS showing the decomposition of gelator 13 to afford the acid derivative; (B) structure of the acid derivative after UV irradiation. Peaks a, b, c, d and e has a mass of 130.2, 34.2, 396.1, 424.2 and 531.2 respectively.
Figure 65. (A) LCMS showing the decomposition of gelator 14 to afford the acid derivative; (B) structure of the acid derivative after UV irradiation. Peaks a, b, c, d and e has a mass of 244.2, 102.2, 368.1, 518.2 and 563.2 respectively.
Table 8. Effect of different pH on the gelators. Compound 13 in DMSO:H₂O (1:9) at 4 mg/mL; Compound 14 in DMSO:H₂O (1:7) at 5 mg/mL; Compound 16 in DMSO:H₂O (1:8) at 4.4 mg/mL; Compound 18 in DMSO:H₂O (1:5) at 6.7 mg/mL.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>pH 7</th>
<th>pH 10</th>
<th>pH 12</th>
<th>pH 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Stable gel</td>
<td>Stable gel</td>
<td>Stable gel</td>
<td>Solution</td>
</tr>
<tr>
<td>14</td>
<td>Stable gel</td>
<td>Stable gel</td>
<td>Solution</td>
<td>Solution</td>
</tr>
<tr>
<td>16</td>
<td>Stable gel</td>
<td>Stable gel</td>
<td>Stable gel</td>
<td>Solution</td>
</tr>
<tr>
<td>18</td>
<td>Stable gel</td>
<td>Stable gel</td>
<td>Solution</td>
<td>Solution</td>
</tr>
</tbody>
</table>
Figure 66. Effect of pH on the gels formed by compounds 12, 13, 16 and 18. All the gels were observed to be stable at both pH 7 and pH 10 after 24 hours. While the gels formed by compounds 16 and 13 were stable in pH 12 after 24 hours, the gels formed by compounds 14 and 18 dissolved in pH 12 after 24 hours. All the gels dissolved in pH 14 after less than 3 hours.
The structure and purity of the compounds were confirmed using $^1$H NMR, $^{13}$C NMR spectroscopy, HRMS and LCMS. The spectra of some representative compounds are shown in Figures 67 and 68.

Compound 14
Figure 67. (A) $^1$H NMR; (B) $^{13}$C NMR and (C) HRMS spectra of compound 14.
Figure 68. (A) $^1$H; (B) $^{13}$C NMR and (C) LCMS spectra of compound 18.

3.3 CONCLUSIONS

In summary, this chapter describes the synthesis and studies of a series of novel carbohydrate-based UV and pH responsive organogels that were able to form gel in a variety of solvents. From this study, $^1$H NMR studies at different temperatures showed that hydrogen bonding and $\pi$-$\pi$ interaction played a role in gelation. The gelators synthesized were stable under neutral conditions but decompose when irradiated with UV light. The gelators were also stable at mild pH solutions but dissolve at higher pH solutions. The compounds reported on herein may be useful for triggered release drug delivery systems by UV irradiation and at higher pH. Future studies will focus on the potential application of the gelators for the release of drugs or dye that is trapped in a gel matrix especially after UV irradiation. Moreover, further investigation will focus on the synthesis of light
responsive gelators that are able to form a spontaneous gel in water hence the UV studies for drug released would be done in a UV cuvette.

3.4 EXPERIMENTAL SECTION

General Experimental Procedures: All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen unless otherwise indicated. Air and moisture-sensitive reagents were handled under nitrogen-conditions. Chromatography was carried out using silica 230-400 mesh silica gel mixed as a slurry with the eluent and columns were packed, rinsed, and run under air pressure. Analytical thin-layer chromatography (TLC) was performed on a pre-coated alumina silica gel. Visualization was either by short wave (254 nm) ultraviolet light, or by staining with phosphomolybdic acid (PMA) followed by brief heating on a hot plate or by a heat gun.

Instrumentation: $^1$H NMR and $^{13}$C NMR were recorded on a Bruker 400 MHz (100 MHz respectively for 13C). Spectra were referenced using CDCl$_3$ as solvents with the residual solvent peak as the internal standard ($^1$H NMR: $\delta$ 7.26 ppm, $^{13}$C NMR: $\delta$ 77.00 ppm for CDCl$_3$. Chemical shifts were reported in parts per million and multiplicities are as indicated: s (singlet), d (doublet), t (triplet,) m (multiplet), br (broad) and dd (doublet of a doublet). Coupling constants, $J$, are reported in Hertz and integration is provided, along with assignments, as indicated. Low-resolution Mass Spectrometry and High Resolution Mass Spectrometry were performed in the Department of Chemistry at Old Dominion University. Melting points were recorded using Stuart Automatic Mel-Temp® capillary melting point apparatus. UV-Vis analysis were performed using Varian 5000 UV-Vis-NIR spectrophotometer.
**Materials and methods.** 2-nitrobenzyl alcohol, succinic anhydride, benzaldehyde dimethyl acetal and 4,5-dimethoxy-2-nitrobenzyl alcohol (Alfa Aesar), 2-nitrobenzyl bromide (Aldrich Chem Co.), N-Acetyl glucosamine (AK Scientific inc), glutaric anhydride (TCI), and meldrum acid (chem inpex int’l inc). Solvents and reagents were obtained commercially and used directly without any further purification. Solvents used for extraction and column chromatography were reagent grade and used as received. All the solvents used for the reaction were purchased from Sigma-Aldrich, VWR, and Fisher. Chromatography was carried out using silica 230-400 mesh silica gel. Thin-layer chromatography (TLC) analysis was performed with Sigma-Aldrich TLC plates, and visualized using UV lamp at 254 nm. \(^1\)H NMR and proton-decoupled \(^{13}\)C NMR spectra were obtained with Bruker 400 MHz spectrometers in CDCl\(_3\). Proton and carbon spectra chemical shifts were reported using CDCl\(_3\) as internal standard at 7.26 ppm and at 77.00 ppm respectively.

**Gelation testing:** In general, about 2 mg of the compounds were tested in a 1 dram vial with a rubber lined screw cap. To this vial, solvents were added in a 0.1 mL increment. A starting concentration of 20 mg/mL was used. The mixture was heated and sonicated until the sample was fully dissolved. The mixture was then allowed to cool at room temperature for 30 mins. The vial was then examined visually. If it appears as a homogenous semi-solid, the vial was then inverted; and if after being inverted, no solvent flows, then the gel is called a stable gel. If the semi-solid like material fell apart while being inverted, it is called an unstable gel. A serial dilution was performed on the stable gel formed until the resulting is no more stable. The concentration prior to the formation of the unstable gel was recorded as the minimum gelation concentration (MGC).

**Rheological Analysis:** The elasticity and stability of the gels were determined by doing rheological analysis. The rheology experiment was performed on a TA Instruments HR-2
Discovery hybrid rheometer, operating in oscillatory mode, with 25 mm stainless steel parallel plate geometry. The Peltier temperature controller was set to maintain a temperature of 25 °C during the measurement. The gels were transferred to the center of the Peltier plate, the gel samples were analyzed immediately with a gap of 100 μm, and dynamic frequency sweep was performed from 0.1 to 100 rad/s with 5% strain.

**Optical microscopy:** A small amount of the stable gels was transferred to a clean glass slide using a spatula or pipette and was observed directly under an optical microscope. Some of the gels were left air dried for a few hours if too much liquid prevent imaging. The gels were observed using the 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 is the CellSens 1.11.

**SYNTHESIS OF SUGAR-BASED LIGHT RESPONSIVE COMPOUNDS**

Compound 4 was obtained as a yellow solid, 1.6 g, 92% yield, mp 173.0-175.0 °C. Rf = 0.3, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl3) δ 7.50-7.48 (m, 2H), 7.37-7.35 (m, 3H), 5.53 (s, 1H), 4.68 (d, $J = 3.6$ Hz, 1H), 4.27 (dd, $J = 4.2$, 9.6 Hz, 1H), 3.84-3.69 (m, 3H), 3.46 (t, $J = 9.2$ Hz, 1H), 3.41 (s, 3H), 2.79 (dd, $J = 3.6$, 9.7 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl3) δ 137.3, 129.2, 128.3, 126.3, 101.9, 101.3, 82.1, 71.8, 69.1, 62.6, 56.7, 55.4; LC-MS m/z [M + H]$^+$ calcd for C$_{14}$H$_{20}$NO$_5$, 282.1; found 282.1.

**SYNTHESIS OF DERIVATIVES OF O-NITROBENZYL ALCOHOL**

Compound 6a, o-Nitrobenzyl Succinate: This was synthesized according to previous report with slight modification.$^{34}$ 2-nitrobenzyl alcohol (1.001 g, 6.530 mmol), succinic anhydride (1.307 g,
13.06 mmol, 2 equiv) and DMAP (0.399 g, 3.26 mmol, 0.05 equiv) were added into a RB flask. 10 mL of chloroform was used as solvent and the reaction was reflux for 24 h under nitrogen atmosphere. The mixture was diluted with chloroform 20 mL and water 15 mL. The organic layer was washed three times with 10 mL 0.1 M HCl. The organic phase was then dried over sodium sulphate and concentrated under reduced pressure. The product was obtain as a brown solid, 1.39 g, 84% yield, mp 71.0-72.0 °C, Rf = 0.3, 20% ethyl acetate/ 80% hexane. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.91 (broad, 1H), 8.09 (dd, $J = 1.0, 8.2$ Hz, 1H), 7.66-7.58 (m, 2H), 7.50-7.46 (m, 1H), 5.55 (s, 2H), 2.74 (s, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 178.1, 171.5, 147.5, 133.7, 131.9, 128.9, 128.8, 125.0, 63.3, 28.8, 28.7; LC-MS m/z [M + Na]$^+$ calcd for C$_{11}$H$_{11}$NO$_6$Na, 276.1; found 276.0.

**Compound 6b**, the compound was synthesized using the same method as used for the synthesis of compound 6a. 4,5-dimethoxy-o-Nitrobenzyl Succinate: 4, 5-dimethoxyl-2-nitrobenzyl alcohol (100 mg, 0.469 mmol), succinic anhydride (93.88 mg, 0.938 mmol, 2 equiv) and DMAP (28.65 mg, 0.235 mmol, 0.05 equiv) were added into a RB flask. 5 mL of chloroform was used as solvent and the reaction was reflux for 24 hrs under nitrogen atmosphere. The mixture was diluted with chloroform 20 mL and water 15 mL. The organic layer was washed three times with 10 mL 0.1 M HCl. The organic phase was then dried over sodium sulphate and concentrated under reduced pressure. The product was obtained as a yellow solid 130 mg, 89% yield, mp 113.0-115.0°C, Rf = 0.6, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.72 (s, 1H), 7.00 (s, 1H), 5.55 (s, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 2.74 (s, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 177.0, 171.5, 153.6, 148.3, 139.9, 126.9, 110.4, 108.3, 63.6, 56.5, 56.4, 28.8, 28.6; LC-MS m/z [M + Na]$^+$ calcd for C$_{13}$H$_{15}$NO$_8$Na, 336.1; found 336.0.
**Compound 8a**, 2-nitrobenzyl glutarate: 2-nitrobenzyl alcohol (500 mg, 3.26 mmol) was dissolved in 10 mL chloroform. Glutaric anhydride (1.12 g, 9.78 mmol, 3 equiv) was added. Mixture was refluxed for 24 h under nitrogen atmosphere. Crude was diluted with 10 mL chloroform and washed three times with 5 mL 0.1M HCl. The Organic phase was dried over sodium sulphate and concentrated under reduced pressure. The product was obtained as a brown solid, 790 mg, 91% yield, mp 53.0-54.0 °C. \( R_f = 0.4, 5\%\text{ MeOH/DCM.} \) \(^1\text{H NMR (400 MHz, CDCl}_3\) \( \delta \) 8.09 (dd, \( J = 1.1, 8.2 \text{ Hz, 1H}), 7.65-7.47 (m, 3H), 5.52 (s, 2H), 2.52 (t, \( J = 7.4 \text{ Hz, 2H}), 2.45 (t, J = 7.4 \text{ Hz, 2H}), 2.05-1.95 (m, 2H); \) \(^{13}\text{C NMR (100 MHz, CDCl}_3\) \( \delta \) 178.8, 172.1, 147.6, 133.6, 131.9, 129.1, 128.8, 125.0, 63.0, 32.9, 32.8, 19.7; LC-MS m/z [M + Na]\(^+\) calcd for C\(_{12}\)H\(_{13}\)NO\(_6\)Na, 290.1; found 290.0.

**Compound 8b**, 4,5-Dimethoxy-2-nitrobenzyl glutarate: 4,5-Dimethoxy-2-nitrobenzyl alcohol (500 mg, 2.46 mmol) was dissolved in 10 mL chloroform. Glutaric anhydride (863 mg, 7.04 mmol, 3 equiv) was added. Mixture was refluxed for 24 hrs under nitrogen atmosphere. Crude was diluted with 10 mL chloroform and washed three times with 5 mL 0.1M HCl. The Organic phase was dried over sodium sulphate and concentrated under reduced pressure. The product was obtained as a yellow solid, 699 mg, 95% yield, mp 87.5-89.0 °C. \( R_f = 0.4, 5\%\text{ MeOH/DCM.} \) \(^1\text{H NMR (400 MHz, CDCl}_3\) \( \delta \) 7.71 (s, 1H), 6.99 (s, 1H), 5.51 (s, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 2.52 (t, \( J = 7.3 \text{ Hz, 2H}), 2.47 (t, J = 7.2 \text{ Hz, 2H}), 2.09-2.01 (m, 2H); \) \(^{13}\text{C NMR (100 MHz, CDCl}_3\) \( \delta \) 178.2, 172.2, 153.5, 148.4, 140.1, 126.8, 126.7, 110.7, 108.3, 63.3, 56.4, 33.1, 32.8, 19.8; LC-MS m/z [M + Na]\(^+\) calcd for C\(_{14}\)H\(_{17}\)NO\(_8\)Na, 350.1; found 350.1.

**Compound 10a**: 2-nitro benzyl alcohol (500 mg, 3.26 mmol, 1 equiv) was dissolved in 6 mL toluene and then meldrum acid (494 mg, 2.58 mmol, 1.05 equiv) was added. The mixture was
refluxed for 4 hours. The reaction was monitored by NMR. After completion of the reaction, the mixture was diluted with 15 mL ethyl acetate and then washed with 10 mL saturated NaHCO₃. The aqueous phase was diluted over sodium sulphate and concentrated to obtain a white solid as product, 593 mg, 76% yield, mp 68.0-69.0 °C. R₇ = 0.3, 5% MeOH/DCM. ¹H NMR (400 MHz, CDCl₃) δ 8.09 (d, J = 8.0 Hz, 1H), 7.65-7.63 (m, 2H), 7.50-7.48 (m, 1H), 5.58 (s, 2H), 3.53 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 170.7, 166.0, 147.3, 133.9, 131.2, 129.0, 125.0, 64.0, 40.9; LC-MS m/z [M + Na]⁺ calcd for C₁₀H₉NO₆Na, 262.0; found 262.1.

**Compound 10b**: 4,5-dimethoxy-2-nitro benzyl alcohol (500 mg, 2.35 mmol, 1 equiv) was dissolved in 6 mL toluene and then meldrum acid (372 mg, 2.58 mmol, 1.1 equiv) was added. The mixture was refluxed for 4 hours. The reaction was monitored by NMR. After completion of the reaction, the mixture was filtered to obtain a yellow precipitate as the product. Obtained 628 mg yellow solid, 89% yield, mp 155.0-156.0 °C, R₇ = 0.2, 5% MeOH/DCM. ¹H NMR (400 MHz, CDCl₃) δ 7.73 (S, 1H), 7.12 (s, 1H), 5.64 (s, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 3.57 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.1, 166.2, 153.8, 148.4, 139.7, 126.5, 110.2, 108.3, 64.3, 56.6, 56.4, 40.8; LC-MS m/z [M + Na]⁺ calcd for C₁₂H₁₃NO₈Na, 322.1; found 322.2.

**GENERAL PROCEDURE FOR THE SYNTHESIS OF COMPOUNDS 12-16**

The acid derivative of 2-nitro benzyl alcohol (0.320 mmol) was dissolved in 1.5 mL of DCM and cool in ice bath for 15 mins. Then oxalyl chloride (0.384 mmol, 1.2 equiv) was added followed by one drop of DMF. Mixture was stirred from 0 °C to rt for 4 hrs to afford the acid chloride. To a solution of compound 4 (75 mg, 0.267 mmol, 1 equiv) in 3 mL of DCM, pyridine (0.065 mL, 0.801 mmol, 3 equiv) was added. Mixture was cool at 0 °C for 15 mins. The acid chloride derivative was
added dropwise over 20 mins and the mixture was stirred at 0 °C for 1 hour and then at rt for 6 hrs. Reaction was monitored by TLC. Reaction mixture was diluted with 15 mL x 2 DCM and washed with 10 mL x 2 saturated ammonium chloride and brine successively. The organic phase was dried over sodium sulphate and then concentrated under reduced pressure. The crude product was purified by flash chromatography using a solvent mixture of hexane:DCM:methanol and the polarity was increased gradually to optimize the separation.

**Compound 12:** The pure product was obtained as a white solid, 110.3 mg, 80% yield, mp 166.0-167.1 °C. R<sub>f</sub> = 0.4, 5% MeOH/DCM. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.09 (dd, <i>J</i> = 1.3 Hz, <i>J</i> = 8.24 Hz, 1H), 7.68-7.64 (m, 1H), 7.61-7.59 (m, 1H), 7.52-7.46 (m, 3H), 7.38-7.34 (m, 3H), 5.98 (d, <i>J</i> = 8.9 Hz, 1H), 5.56 (s, 1H), 5.53 (d, <i>J</i> = 2.5 Hz, 2H), 4.69 (d, <i>J</i> = 3.8 Hz, 1H), 4.30-4.20 (m, 2H), 3.89 (t, <i>J</i> = 9.5 Hz, 1H), 3.83-3.74 (m, 2H), 3.58 (t, <i>J</i> = 9.0 Hz, 1H), 3.40 (s, 3H), 2.81 (t, <i>J</i> = 6.8 Hz, 2H), 2.58 (t, <i>J</i> = 6.7 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 172.5, 172.4, 137.2, 133.8, 131.9, 129.2, 128.8, 128.3, 126.3, 125.0, 101.9, 98.9, 81.9, 70.6, 68.9, 63.3, 62.4, 55.3, 54.2, 30.9, 29.4; HRMS (ESI) m/z: [M + Na]<sup>+</sup> calcd for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>10</sub>Na, 539.1636; found, 539.1630.

**Compound 13:** Obtained a white solid, 117.6 mg, 83% yield. mp 126.0-128.4 °C. R<sub>f</sub> = 0.4, 5% MeOH/DCM. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.08 (dd, <i>J</i> = 1.2, 8.3 Hz, 1H), 7.67-7.63 (m, 1H), 7.58 (d, <i>J</i> = 7.4 Hz, 1H), 7.51-7.47 (m, 3H), 7.37-7.34 (m, 3H), 5.96 (d, <i>J</i> = 8.8 Hz, 1H), 5.56 (s, 1H), 5.50 (s, 2H), 4.72 (d, <i>J</i> = 3.8 Hz), 4.29-4.20 (m, 2H), 3.88 (t, <i>J</i> = 8.9 Hz, 1H), 3.79-3.74 (m, 2H), 3.60-3.56 (m, 1H), 3.40 (s, 3H), 2.5 (t, <i>J</i> = 7.0 Hz, 2H), 2.34 (t, <i>J</i> = 7.2 Hz, 2H), 2.06-1.99 m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 173.3, 172.6, 137.1, 133.7, 131.8, 129.5, 129.2, 129.0, 128.2, 126.3, 125.0, 101.9, 98.8, 70.7, 68.8, 63.1, 62.4, 55.3, 54.0, 35.2, 32.9, 20.7; HRMS (ESI) m/z:
[M + Na]$^+$ calcd for C$_{26}$H$_{30}$N$_2$O$_{10}$Na, 553.1793; found, 553.1786; HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{26}$H$_{30}$N$_2$O$_{10}$Na, 553.1793; found, 553.1786.

**Compound 14**: The product eluted around 1.3% MeOH/DCM/hexane mixture. Obtained a yellow solid, 105 mg, 70% yield, mp 204.0-205.5 °C. R$_f$ = 0.5, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.72 (S, 1H), 7.50-7.47 (m, 2H), 7.37-7.35 (m, 3H), 7.08 (s, 1H), 7.04 (d, $J = 8.7$ Hz, 1H), 5.59 (d, $J = 4.4$ Hz, 2H), 5.55 (s, 1H), 4.74 (d, $J = 3.8$ Hz, 1H), 4.30-4.21 (m, 2H), 4.01 (s, 3H), 3.98-3.93 (m, 1H), 3.95 (s, 3H), 3.82-3.74 (m, 2H), 3.58 (t, $J = 7.1$ Hz, 1H), 3.49 (s, 2H), 3.41 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 168.0, 165.8, 153.8, 148.4, 139.8, 137.0, 129.2, 128.3, 126.3, 126.2, 110.6, 108.2, 102.0, 98.7, 81.9, 70.3, 68.8, 64.2, 62.4, 56.7, 56.4, 55.4, 54.2, 41.8. HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{26}$H$_{30}$N$_2$O$_{12}$Na, 585.1691; found, 585.1683.

**Compound 15**: The pure product was obtained as a yellow solid, 72.8 mg, 73%, mp decomposed around 220 °C. R$_f$ = 0.5, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71 (s, 1H), 7.45-7.43 (m, 2H), 7.35-7.34 (m, 3H), 7.05 (m, 1H), 5.90 (d, $J = 9.7$ Hz, 1H), 5.58 (s, 1H), 5.53 (d, $J = 5.5$ Hz, 2H), 5.39 (t, $J = 10.0$ Hz, 1H), 4.67 (d, $J = 3.6$ Hz, 1H), 4.37-4.28 (m, 2H), 4.04 (s, 3H), 3.95 (s, 3H), 3.89-3.85 (m, 1H), 3.79 (t, $J = 10.0$ Hz, 1H), 3.72 (t, $J = 9.4$ Hz, 1H), 3.41 (s, 3H), 2.76 (t, $J = 6.9$ Hz, 2H), 2.53-2.49 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.1, 171.2, 160.9, 153.8, 148.1, 139.7, 136.8, 129.2, 128.2, 127.3, 126.2, 110.2, 108.2, 101.7, 99.0, 78.8, 69.9, 68.8, 63.4, 62.8, 56.6, 56.4, 55.4, 52.1, 30.6, 29.1; HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{27}$H$_{32}$N$_2$O$_{12}$Na, 599.1847; found, 599.1843.
Compound 16 The pure product was obtained as a yellow solid, 100 mg, 88% yield. mp 177.1-
178.0 °C. Rf = 0.4, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.70 (s, 1H), 7.50-7.47 (m, 2H), 7.37-7.34 (m, 3H), 6.99 (s, 1H), 5.97 (d, J = 8.8 Hz), 5.55 (s, 1H), 5.47 (s, 2H), 4.71 (d, J =
3.8 Hz, 1H, H-1), 4.27 (dd, J = 2.4 Hz, J = 7.7 Hz, 1H, H-6a), 4.24-4.18 (m, 1H, H-2), 3.97 (s, 3H), 3.94(s, 3H), 3.87 (t, J = 9.6 Hz, 1H, H-3), 3.79-3.76 (m, 2H, H-6b, H-5), 3.57 (dd, J = 4.4 Hz, J = 9.0 Hz, 1H, H-4), 3.39 (s, 3H), 2.50 (t, J = 7.0 Hz, 2H), 2.34 (t, J = 7.2 Hz, 2H), 2.06-1.98 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.3, 172.7, 153.5, 148.5, 140.2, 137.1, 129.2, 128.3, 126.6, 126.3, 111.1, 108.4, 101.9, 98.9, 82.0, 68.9, 63.5, 62.4, 56.5, 56.4, 55.3, 54.0, 35.2, 33.0, 20.8;
HRMS (ESI) m/z: [M + Na]$^+$ calcd for C$_{28}$H$_{34}$N$_2$O$_1$2Na, 613.2004; found, 613.1996.

Compound 17: Compound 4 (500 mg, 1.78 mmol, 1 equiv) was dissolved in 15 mL DCM. Then
K$_2$CO$_3$ (737 mg, 5.33 mmol, 3 equiv) was added. The mixture was stirred in ice for 20 mins.
Bromoacetyl chloride (0.16 mL, 1.96 mmol, 1.1 equiv) was dissolved in 1 mL of DCM and added
drop-wise to the reaction mixture. The reaction was stirred in ice for 1 hr and then at rt for 7 h.
TLC and NMR shows that the sugar starting material has been consumed. Reaction mixture was
diluted with 20 mL DCM and then washed with 15 mL water, sat. NaHCO$_3$ and brine respectively.
The organic phase was dried over sodium sulphate and concentrated. Obtained a pure yellow solid
without further purification, 676 mg, 1.68 mmol, 95% yield, mp decomposed on heating. Rf = 0.6,
5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.50-7.48 (m, 2H), 7.39-7.36 (m, 3H), 6.77 (d, J =
9.0 Hz, 1H), 5.56 (s, 1H), 4.74 (d, J = 3.8 Hz, 1H), 4.30 (dd, J = 3.8, 9.2 Hz, 1H), 4.24-4.19 (m, 1H), 3.98 (d, J = 8.9 Hz, 1H), 3.95-3.88 (m, 2H), 3.83-3.75 (m, 2H), 3.59 (t, J = 9.0 Hz, 1H), 3.44 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.5, 137.0, 129.3, 128.3, 126.3, 102.0, 98.7, 81.9, 70.3, 68.8, 62.4, 55.5, 54.4, 29.0; LC-MS m/z [M + H]$^+$ calcd for C$_{16}$H$_{21}$BrNO$_6$, 402.1; found 402.0.
**GENERAL PROCEDURE FOR THE SYNTHESIS OF COMPOUNDS 18-23**

Compound 4 (100 mg, 0.249 mmol, 1 equiv) was dissolved in 5 mL of solvent followed by DIEA (0.06 mL, 0.323 mmol, 1.3 equiv) and then the acid derivative (0.273 mmol, 1.1 equiv) was added. The reaction mixture was heated for 6 hours. TLC and LCMS shows that the sugar starting material has been consumed. Mixture was concentrated and diluted with 15 mL DCM and washed with 7 mL saturated NaHCO₃ and water respectively. Organic phase was dried over sodium sulphate and then concentrated under reduced pressure. The crude product was purified by flash chromatography using a solvent mixture of DCM:hexane:methanol.

**Compound 18** was obtained as a yellow solid, 113 mg, 0.202 mmol, 81%, mp 162.0-163.0 °C. Rᵣ = 0.5, 5% MeOH/DCM. ¹H NMR (400 MHz, CDCl₃) δ 8.11 (dd, J = 1.2, 8.2 Hz, 1H), 7.69-7.65 (m, 1H), 7.60 (d, J = 7.9Hz, 1H), 7.53-7.49 (m, 3H), 7.39-7.34 (m, 3H), 6.84 (d, J = 8.6Hz ,1H), 5.62-5.61 (m, 2H), 5.56 (s, 1H), 4.75 (d, J = 3.7 Hz, 1H), 4.77-4.69 (m, 2H), 4.30-4.20 (m, 2H), 3.95 (t, J = 9.8 Hz, 2H), 3.82-3.74 (m, 3H), 3.61 (s, 1H), 3.38 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.5, 166.4, 164.6, 147.7, 137.2, 133.9, 130.7, 129.5, 129.4, 129.2, 128.3, 126.3, 125.3, 102.0, 98.7, 81.9, 69.8, 68.9, 64.5, 63.9, 63.4, 62.4, 55.4, 54.0, 40.9; LC-MS m/z [M + H]⁺ calcd for C₂₆H₂₉N₂O₁₂, 561.2; found 561.2.

**Compound 19** was obtained a white solid, 121 mg, 0.63 mmol, 85%, mp 164.0-166.0 °C. Rᵣ = 0.5, 5% MeOH/DCM. ¹H NMR (400 MHz, CDCl₃) δ 8.07 (dd, J = 1.1, 8.2 Hz, 1H), 7.64-7.56 (m, 2H), 7.50-7.46 (m, 3H), 7.37-7.33 (m, 3H), 6.57 (d, J = 8.8 Hz, 1H), 5.57 (s, 1H), 5.55 (s, 2H), 4.74 (d, J = 3.8 Hz, 1H), 4.69-4.60 (m, 2H), 4.30-4.21 (m, 2H), 3.99 (t, J = 9.9 Hz, 1H), 3.85-3.75 (m, 2H), 3.59 (t, J = 9.1 Hz, 1H), 3.39 (s, 3H), 2.83-2.73 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 172.1, 171.0, 167.9, 147.6, 137.2, 133.8, 131.3, 129.5, 129.2, 129.1, 128.3, 126.3, 125.1, 102.0,
98.7, 81.8, 69.7, 68.9, 63.7, 63.2, 62.5, 55.4, 53.9, 29.0, 28.9; LC-MS m/z [M + H]$^+$ calcd for C$_{27}$H$_{31}$N$_2$O$_{12}$, 575.2; found 575.2.

**Compound 20** was obtained as a brown solid, 123 mg, 0.210 mmol, 84%, mp 112.0-114.0 °C. R$_f$ = 0.5, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.08 (dd, J = 1.2, 8.3 Hz, 1H), 7.66-7.62 (m, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.50-7.46 (m, 3H), 7.38-7.34 (m, 3H), 6.47 (d, J = 8.9 Hz, 1H), 5.56 (s, 1H), 5.51 (s, 2H), 4.75 (d, J = 3.8 Hz, 1H), 4.62 (s, 2H), 4.30-4.23 (m, 2H), 3.95 (t, J = 9.2 Hz, 1H), 3.81-3.74 (m, 2H), 3.61-3.57 (m, 1H), 3.40 (s, 3H), 2.55-2.50 (m, 4H), 2.07-2.02 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.2, 171.4, 167.9, 147.8, 137.1, 133.7, 131.6, 129.5, 129.2, 129.1, 128.3, 126.3, 125.1, 102.0, 98.7, 81.9, 70.1, 68.8, 63.2, 62.9, 62.5, 55.4, 53.7, 32.9, 32.8, 19.9; LC-MS m/z [M + H]$^+$ calcd for C$_{28}$H$_{33}$N$_2$O$_{12}$, 589.2; found 589.2.

**Compound 21** was obtained as a yellow solid 124 mg, 0.2 mmol, 81%, mp 180.0-181.0 °C. R$_f$ = 0.5, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.73 (s, 1H), 7.50-7.48 (m, 2H), 7.38-7.35 (m, 3H), 7.02 (s, 1H), 6.78 (d, J = 8.7 Hz, 1H), 5.61 (s, 2H), 5.55 (s, 1H), 4.76-4.67 (m, 3H), 4.29-4.20 (m, 2H), 3.97 (m, 3H), 3.91 (s, 3H), 3.83-3.73 (m, 3H), 3.62 (s, 3H), 3.39 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.4, 166.2, 164.9, 153.8, 148.7, 140.0, 137.1, 129.2, 128.3, 126.3, 125.6, 110.9, 108.4, 102.0, 98.7, 81.9, 69.7, 68.9, 64.8, 63.4, 62.4, 56.7, 56.4, 55.5, 53.9, 41.0; LC-MS m/z [M + H]$^+$ calcd for C$_{28}$H$_{33}$N$_2$O$_{14}$, 621.2; found 621.2.

**Compound 22** was obtained as a yellow solid, 142 mg, 0.224 mmol, 90% yield, mp 214.0-215.0 °C. R$_f$ = 0.5, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.69 (s, 1H), 7.48-7.46 (m, 2H), 7.36-7.31 (m, 3H), 6.98 (s, 1H), 6.55 (d, J = 8.9 Hz, 1H), 5.58-5.50 (m, 3H), 4.74 (d, J = 3.7 Hz, 1H), 4.68-4.59 (m, 2H), 4.29-4.20 (m, 2H), 3.98-3.96 (m, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.81-
3.73 (m, 2H), 3.58 (t, J = 9.0 Hz, 1H), 3.40 (s, 3H), 2.81-2.76 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.2, 171.2, 167.8, 153.6, 148.5, 140.0, 137.1, 129.2, 128.3, 126.3, 110.8, 108.4, 102.0, 98.7, 81.8, 69.8, 68.9, 64.0, 63.2, 62.4, 56.5, 56.4, 55.4, 53.9, 29.0, 28.9; LC-MS m/z [M + H]$^+$ calcd for C$_{29}$H$_{35}$N$_2$O$_{14}$, 635.2; found 635.2.

**Compound 23** was obtained as a yellow solid, 129 mg, 0.200 mmol, 80%, mp 202.0-204.0 °C. $R_f$ = 0.5, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.70 (s, 1H), 7.49-7.47 (m, 2H), 7.36-7.35 (m, 3H), 6.98 (s, 1H), 6.46 (d, J = 8.7 Hz, 1H), 5.56 (s, 1H), 5.49 (s, 2H), 4.75 (d, J = 3.7 Hz, 1H), 4.65-4.57 (m, 2H), 4.29-4.25 (m, 2H), 3.98-3.94 (m, 7H), 3.81-3.77 (m, 2H), 3.59 (t, J = 9.0 Hz, 1H), 3.41 (s, 3H), 2.56-2.51 (m, 4H), 2.06-2.02 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.3, 171.4, 167.9, 153.5, 148.5, 140.3, 137.1, 129.2, 128.3, 126.4, 126.3, 111.2, 108.4, 102.0, 98.7, 81.9, 70.1, 68.9, 63.6, 62.9, 62.5, 56.5, 56.4, 55.4, 53.7, 33.0, 32.8, 19.9; LC-MS m/z [M + H]$^+$ calcd for C$_{30}$H$_{37}$N$_2$O$_{14}$, 649.2; found 649.2.
4.1. INTRODUCTION

Low molecular weight gelators (LMWGs) are a new class of advanced soft materials that have gained great attention over the past few decades due to their valuable properties and diverse applications. Carbohydrate and natural product based low molecular based gelators (LMWGs) are invaluable compounds in the field of soft materials and biomedical chemistry. The structure of LMWGs is comprised of a self-assembled, three-dimensional cross-linked network of gelator molecules that are bounded by non-covalent forces. Glucosamine and N-acetyl glucosamine as shown in Figure 69 are naturally present in many organisms. They are naturally occurring amino sugars that have found application for wound healing. Glucosamine has found application as a dietary supplement for supporting function and structure of joints. It is also used as one of the main ingredient to relieve osteoarthritis.

![Figure 69. Structures of Glucosamine and N-acetyl glucosamine.](image-url)
There have been many research publications on the application of glucosamine for gelation. In 2007, Bin Xu research group formed a hydrogel (compounds 3 and 4) at 2 mg/mL by linking D-glucosamine with L/D-phenylalanine and naphthyl group. The structures of both compounds are shown in Figure 70. The gels were observed to have both stable and elastic properties as observed using rheology.

The biocompatibilities of the gels were examined as this is an important requirement for the gels to be used for biomedical applications. The analysis was done in a cytotoxicity assay of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) which showed that compound 3 showed 73.8% Hela cell survival in 100 µM in 24 hours while compound 4 showed 79.0% at the same condition. Based on the above results, compound 4 was used in wound healing experiment using a mouse model. The result showed that a mouse treated with gel showed much faster healing and smaller scar when compared with a controlled group.

Figure 70. Structures of glucosamine based hydrogelators.
Over the past decade, our group has been studying the gelation abilities of the derivatives of D-glucosamine including triazole, esters, carbamates, amides, and ureas. Using benzaldehyde dimethylacetal to protect the free hydroxyl groups on C-4 and C-6 on methyl-2-acetamido-2-deoxy-α-D-glucopyranoside followed by deprotection yielded 4, 6-benzylidene acetal protected headgroup 5 (Figure 71). Compound 5 was subsequently converted to the corresponding amide and urea derivatives. The R group included straight chain alkyl, terminal alkyne, and aromatic rings. The gelation properties of the derivatives were evaluated in various solvents including DCM, THF, water, ethanol, hexane, isopropanol and aqueous solution of ethanol and DMSO. Both the amide and the urea derivatives were effective gelators in aqueous solvent. While the aromatic derivative of the amide group formed a hydrogel at 2 mg/mL, the alcohol derivative of the urea group was also able to form a hydrogel at 2.2 mg/mL. Both the amide and the urea derivatives did not form gel in DCM and THF. Interestingly, the amide derivatives were able to form a stable gel in hexane. But no derivative of the urea formed a gel in hexane.

Figure 71. Structures of sugar head group, the amide and urea derivatives.

As described previously, one of the challenges in gelation study is its difficulty to predict the gelation abilities of compounds. Gaining more understanding on the structure-gelation relationship has become vital in the field of supramolecular chemistry. To gain more insight as to what role the anomeric position plays in influencing gelation, another study was performed. The anomeric
substituent was changed from the $\alpha$-methoxy to $\alpha$-ethoxy group and the gelation ability was examined (Figure 72). The gelation properties of the derivatives were evaluated in various solvents including water, ethanol, hexane, toluene, isopropanol and aqueous solution of ethanol and DMSO. The short chain terminal alkyne derivative did not form gel in most of the solvent tested except in toluene and water. None of the derivatives formed gel in alcohol solvents tested. Moreover, only the pentyl derivative formed gel in hexane.

![Structures of $\alpha$-ethoxy sugar head group, the amide derivatives.](image)

With these result, we seek to further probe the influence of the aromatic position on gelation by attaching the butoxy group to the anomeric position. The amide and urea derivatives of the headgroup were synthesized and their gelation abilities were studies.

4.2. RESULTS AND DISCUSSION

SYNTHESIS OF COMPOUND 12 AND ITS DERIVATIVES

The headgroup was synthesized from the starting material as shown in Scheme 19. The first step in the synthesis of compound 12 is the glycosylation of N-acetyl-glucosamine, 2 by treating it with $n$-butanol in the presence of acidic ion exchange resin. This reaction afforded compound 10, the butyl glycoside in 96% yield. The next step was the protection of the C-4 and C-6 hydroxyl
groups of 10 with benzaldehyde dimethylacetal to afford the acetal-protected analog 11 in 80% yield. Finally, the head group 12 was then synthesized by deprotecting the 2-amino group.

**Scheme 19.** Synthesis of 4, 6-O-benzylidene-α-butyl-D-glucosamine.

The amides derivatives with the general structure 13 were synthesized by reacting the head group, 12 in slightly excess acyl chlorides in the presence of pyridine using DCM as solvent (**Scheme 20**). Urea with the general structure 22 were synthesized by reacting head group, 12 with various isocyanates (**Scheme 21**). The choice of acyl chlorides and isocyanates were based on the availability of starting materials and from the results of our previous studies of urea and amide with the general structures 6, 7 and 9. All the compounds synthesized were purified by column chromatography using a solvent mixture of MeOH/DCM.

A series of 8 amide derivatives were synthesized ranging from a simple alkyl straight chain derivatives to alkyne derivatives. Others are alkyl halides, acids, benzoyl and pyrene derivatives as shown in **Scheme 20**. The acyl chlorides of compounds 14 and 21 were synthesized in situ.
**Scheme 20.** Synthesis of amide derivatives.

A series of 6 urea derivatives were also synthesized as shown in **Scheme 21** ranging from straight chain alkyl (C5-C7), cyclo hexyl, phenyl and benzyl derivatives. The gelation tests of the amide and urea derivatives were performed in various solvent; water, ethanol, IPA, THF, hexane and aqueous solution. The gelation test table for the amide derivatives is shown in Table 9. None of the compounds formed effective gelator in the non-polar solvent, hexane. They all were insoluble in hexane. From the gel test table, it was observed that the acetal protected compound 11 formed the best performing hydrogel at a concentration of 5 mg/mL. It also formed a gel in an aqueous solution of DMSO:H₂O at 5 mg/mL. The straight chain alkyl compounds 14, 15, straight chain terminal alkyne compound 16, and the alkyl halide compounds 17, 18 formed organogels in ethanol while the other compounds either formed a solution or were insoluble in ethanol. For
EtOH:H$_2$O (1:2) solvent, only compounds 14 and 18 formed an organogel. Moreover, all of the compound tested formed gel in DMSO:H$_2$O (1:2) except compounds 12 and 21.

**Scheme 21.** Synthesis of urea derivatives.

![Scheme 21](image)

Table 10 shows the gelation test table for the urea derivatives. Again, none of the compounds formed effective gelator in the non-polar solvent, hexane and water. They all were insoluble in hexane and water. From the gel test table, it was observed that most of the compounds were effective gelators in a mixture of DMSO:H$_2$O and EtOH:H$_2$O. However, only compound 23 and 28 was able to form gel in a mixture of EtOH:H$_2$O (1:2) at 5.0 mg/mL and 6.7 mg/mL respectively. Only compounds 27 and 28 formed a gel in pure ethanol at 20 mg/mL. From all the gelators tested in IPA, only compounds 28 formed a gel. The ability of compound 28 to form gel in a range of solvents can be attributed to an increased $\pi$-$\pi$ interaction during self-assemble.
The elasticity and stability of the gels formed by the amide derivatives were also determined using the dynamic rheology sweep. As shown in Figure 73, the dynamic moduli $G'$ and $G''$ were plotted as a function of angular frequency $\omega$ at the minimum gelation concentration of the gels. For all the compounds, the storage modulus $G'$ was greater than the loss modulus $G''$ at all tested frequencies. This is an indication of the gel’s elastic properties. The gel pictures of some of the gels formed are shown in Figure 74.

**Table 9.** Gelation test results for the amide derivatives with the general structure.

<table>
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<th>Compound number</th>
<th>Toluene</th>
<th>i-PrOH</th>
<th>EtOH</th>
<th>EtOH: H$_2$O (1:1)</th>
<th>EtOH: H$_2$O (1:2)</th>
<th>DMSO: H$_2$O (1:1)</th>
<th>DMSO: H$_2$O (1:2)</th>
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<td>G 10.0</td>
<td>S</td>
<td>S</td>
<td>G 10.0</td>
<td>P</td>
<td>G 10.0</td>
<td>G 5.0</td>
<td>G 5.0</td>
</tr>
<tr>
<td>12</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>P</td>
<td>P</td>
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<tr>
<td>14</td>
<td>S</td>
<td>S</td>
<td>G 10.0</td>
<td>G 6.7</td>
<td>G 20.0</td>
<td>G 10.0</td>
<td>G 20.0</td>
<td>I</td>
</tr>
<tr>
<td>15</td>
<td>S</td>
<td>S</td>
<td>G 10.0</td>
<td>S</td>
<td>P</td>
<td>G 20.0</td>
<td>P</td>
<td>I</td>
</tr>
<tr>
<td>16</td>
<td>G 20.0</td>
<td>G 20.0</td>
<td>G 20.0</td>
<td>G 4.0</td>
<td>I</td>
<td>G 4.0</td>
<td>G 20.0</td>
<td>I</td>
</tr>
<tr>
<td>17</td>
<td>S</td>
<td>G 20.0</td>
<td>G 20.0</td>
<td>G 10.0</td>
<td>I</td>
<td>G 10.0</td>
<td>G 10.0</td>
<td>I</td>
</tr>
<tr>
<td>18</td>
<td>G 10.0</td>
<td>G 10.0</td>
<td>G 20.0</td>
<td>G 5.0</td>
<td>G 6.7</td>
<td>G 5.0</td>
<td>G 5.0</td>
<td>I</td>
</tr>
<tr>
<td>19</td>
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<td>S</td>
<td>S</td>
<td>I</td>
<td>S</td>
<td>G 10.0</td>
<td>G 10.0</td>
<td>I</td>
</tr>
<tr>
<td>20</td>
<td>S</td>
<td>S</td>
<td>I</td>
<td>G 3.3</td>
<td>I</td>
<td>P</td>
<td>G 5.0</td>
<td>I</td>
</tr>
<tr>
<td>21</td>
<td>S</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>I</td>
<td>P</td>
<td>I</td>
<td>I</td>
</tr>
</tbody>
</table>

G, gel at room temperature; the numbers are the corresponding minimum gelation concentrations (MGCs) in mg/mL. I, insoluble. P, precipitate. S, soluble at $\sim$20 mg/mL. All the compounds were insoluble in hexane.
The elasticity and stability of the gels formed by the urea derivatives were also determined using the dynamic rheology sweep. As shown in Figure 75, the dynamic moduli $G'$ and $G''$ were plotted as a function of angular frequency $\omega$ at the minimum gelation concentration of the gels. For all the compounds, the storage modulus $G'$ was greater than the loss modulus $G''$ at all tested frequencies. This is an indication of the gel’s elastic properties. Interestingly, the urea derivatives have a stronger elasticity when compared to the amide derivative as it has a bigger storage modulus.
Table 10. Gelation test results for the series of urea derivatives with the general structure.

<table>
<thead>
<tr>
<th>Compound number</th>
<th>Toluene</th>
<th>i-PrOH</th>
<th>EtOH</th>
<th>EtOH: H$_2$O (1:1)</th>
<th>EtOH: H$_2$O (1:2)</th>
<th>DMSO: H$_2$O (1:1)</th>
<th>DMSO: H$_2$O (1:2)</th>
<th>H$_2$O</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>G 20.0</td>
<td>S</td>
<td>S</td>
<td>G 10.0</td>
<td>G 5.0</td>
<td>G 5.0</td>
<td>G 3.3</td>
<td>I</td>
</tr>
<tr>
<td>24</td>
<td>G 20.0</td>
<td>S</td>
<td>S</td>
<td>G 10.0</td>
<td>I</td>
<td>G 3.3</td>
<td>G 10.0</td>
<td>I</td>
</tr>
<tr>
<td>25</td>
<td>P</td>
<td>S</td>
<td>S</td>
<td>G 5.0</td>
<td>I</td>
<td>G 2.2</td>
<td>G 5.0</td>
<td>I</td>
</tr>
<tr>
<td>26</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>G 2.5</td>
<td>P</td>
<td>G 4.0</td>
<td>G 4.0</td>
<td>I</td>
</tr>
<tr>
<td>27</td>
<td>G 20.0</td>
<td>P</td>
<td>G 20.0</td>
<td>P</td>
<td>I</td>
<td>G 2.5</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>28</td>
<td>G 10.0</td>
<td>G 10.0</td>
<td>G 20.0</td>
<td>G 1.8</td>
<td>G 6.7</td>
<td>G 3.3</td>
<td>G 4.0</td>
<td>I</td>
</tr>
</tbody>
</table>

G, gel at room temperature; the numbers are the corresponding minimum gelation concentrations (MGCs) in mg/mL. I, insoluble. P, precipitate. S, soluble at ~20 mg/mL. All the compounds were insoluble in hexane.

The optical micrographs of the several tested gels were also studied. The gels formed interesting and unique morphologies. The gelators formed self-assembled fibrous network as shown in Figure 76. The morphology of the gel formed by gelator 16 formed both a thin, a thick and uniform fibrous network (Figure 76a and 76b). The gel formed by compound 20 formed a more dense fibrous network (Figure 76c) when observed at a lower magnification. For compound 23, the morphology shows the formation of a planner sheet as shown in Figures 76 (e and f). The gel formed by compound 25 formed a more thick long fibrous network at a higher magnification.
Figure 74. a) An opaque gel formed by compound \textbf{11} in H$_2$O at 5.0 mg/mL; b) An opaque gel formed by compound \textbf{25} in DMSO:H$_2$O (v1:1) at 2.2 mg/mL; c) An opaque gel compound \textbf{28} in EtOH:H$_2$O (v1:1) at 1.8 mg/mL; d) A transparent gel compound \textbf{28} in DMSO:H$_2$O (v1:1) at 3.3 mg/mL.

In order to understand the self-assembling process and the effect of hydrogen bonding in compound \textbf{11}, \textsuperscript{1}H-NMR studies at different temperatures using CDCl$_3$ was performed. This is shown in Figure 77. The NH peak in compound \textbf{11} as shown in Figure 77 shifted upfield from 5.83 ppm to 5.77 ppm upon increasing the temperature from 30 °C to 55 °C. This upfield shift shows a reduction in the intermolecular hydrogen bonding between the compounds as temperature increases. The anomeric proton also shifted slightly from 4.82 ppm to 4.83 ppm. The acetal proton however did not experience any shift at higher temperatures. Based on this study, it can be deduced that the chemical shift changes at higher temperatures are due to the change of the hydrogen bonding interactions of the amide group. This indicated that hydrogen bonding are important for the molecule self-assembly and may impact the gelation behavior.
Figure 75. Rheology properties of the gels formed by compounds 23, 24 and 28 in DMSO:H₂O. Compound 23 is in DMSO:H₂O (1:1) at 5.0 mg/mL; compound 24 is in DMSO:H₂O (1:1) at 3.3 mg/mL and compound 28 is in DMSO: H₂O (1:2) at 5 mg/mL. The applied strain was 5%. 
Figure 76. The optical micrographs of the gel samples in EtOH:H$_2$O. a and b) compound 16 (v 1:1), 4.0 mg/mL at 100 µm and 50 µm; c and d) compound 20 (v 1:1), 3.3 mg/mL at 50 µm and 20 µm; e and f) compound 23 (v 1:2), 5.0 mg/mL at 50 µm; g and h) compound 25 (v 1:1), 5.0 mg/mL at 20 µm and 10 µm respectively.
The $^1$H NMR spectra of compound 11 at the variable concentrations at 30 °C was also investigated as shown in Figure 78. Unlike what was observed in the temperature dependent studies, the NH peak showed a slight downfield shield at higher concentration. The downfield shift of the amide proton signal at higher concentration shows that the hydrogen bonding plays a role in gelation as it shows a more increased interaction at a higher concentration.

**Figure 77.** $^1$H-NMR spectra at variable temperature of compound 11 from 30 °C to 55 °C in CDCl$_3$. 
Figure 78. $^1$H-NMR spectra at variable concentration of compound 11 in CDCl$_3$. The amide peak shifted from 5.81 at 4 mg/mL to 5.85 ppm at 16 mg/mL.

In order to understand the self-assembling process and the effect of hydrogen bonding of urea in compound 28, $^1$H-NMR studies at different temperatures using DMSO-d$_6$ was performed. This is shown in Figure 79. The NH peak of the urea close to the benzyl substituent in compound 28 shifted upfield from 6.58 ppm to 6.56 ppm upon increasing the temperature from 30 °C to 60 °C. The other NH peak shifted upfield also from 5.19 ppm to 5.03 ppm. This shift shows a reduction in the intermolecular hydrogen bonding between the compounds as temperature increases. The anomeric proton also shifted slightly from 4.75 ppm to 4.78 ppm. The acetal proton however did not experience any significant shift at higher temperatures. The OH peak also shifted upfield from 5.82 ppm to 5.74 ppm. Based on this study, it can be deduced that the chemical shift changes at
higher temperatures are due to the change of the hydrogen bonding interactions of the amide group. This indicated that hydrogen bonding are important for the molecule self-assembly and may impact the gelation behavior.

**Figure 79.** $^1$H-NMR spectra at variable concentration of compound 28 from 30 °C to 60 °C in CDCl$_3$.

**Drug release study**

The biological application of the hydrogel formed by compound 11 for drug delivery was studied. A non-steroidal anti-inflammatory drug (NSAID), naproxen was used for this study and the release profile of both the drug trapped in the gel matrix was determined. UV spectroscopy was used to monitor the release profile of the drug at room temperature. The hydrogel formed by compound
was selected for the study and the release profile of naproxen drug from the gel matrix in the presence of water (pH 7) was monitored at different time intervals. For the estimated amount of naproxen released from a gel matrix, the gel was prepared in a 1 mL dram vial using compound 11, 2 mg in a 0.4 mL solution of 0.50 mg naproxen in water. After a stable gel was formed, the gel was allowed to age for 12 h. 3.0 mL of water (pH 7) was added on top of the gel carefully (Figure 80). The estimated amount of naproxen released from the gel matrix into the aqueous solution was monitored by UV absorption at various time. The naproxen standard was measured using a 3.4 mL solution of 0.50 mg of naproxen sodium in water (pH 7).

As shown in Figures 81 naproxen was slowly released from the gel matrix to the neutral aqueous phase (pH 7). 49% of the naproxen drug was released into the aqueous phase after 1 hour. The amount of the drug released into the aqueous phase increased with time as about 94% of naproxen was released after 7 hours (Table 11).

Table 11. Table showing the rate of release of naproxen drug to the aqueous phase

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Estimated naproxen drug released (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>94</td>
</tr>
<tr>
<td>Standard</td>
<td>100</td>
</tr>
</tbody>
</table>
**Figure 80.** A hydrogel formed by compound 11 (2 mg), naproxen sodium (0.5 mg) were dissolved in 0.4 mL water. 3 mL of pH7 solution added on top of the gel. The picture shows that the gel is stable.

**Figure 81.** UV spectrum showing the released naproxen sodium drug from the gel matrix formed by compound 11 to the aqueous phase
Dye absorption studies

A hydrogel formed by compound **11** in 5 mg/mL was analyzed for its ability to absorb rhodamine B base dye. Compound **11**, 10 mg was dissolved in 2.0 mL of water, heated and cooled to form a hydrogel at 5 mg/mL in a 1 mL dram vial. After the formation of the stable hydrogel, a 2 mL solution of 0.02 mM of rhodamine B base in water was added to the top of the gel. Absorption of rhodamine B base from the aqueous solution to the hydrogel matrix was monitored by UV-Vis spectroscopy at different time intervals. The UV-Vis spectrum is shown in Figure 82. A table for the amount of rhodamine B base left in the aqueous solution at different time point is also shown in Table 12 and the gel pictures is shown in Figure 83 at different time point.

**Table 12.** Table showing the absorption of rhodamine B base into the gel matrix from the aqueous phase.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount of rhodamine in solution</th>
<th>Amount of rhodamine in solution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>2.094</td>
<td>93</td>
</tr>
<tr>
<td>16</td>
<td>1.760</td>
<td>78</td>
</tr>
<tr>
<td>24</td>
<td>1.627</td>
<td>72</td>
</tr>
<tr>
<td>32</td>
<td>1.571</td>
<td>70</td>
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<tr>
<td>48</td>
<td>1.334</td>
<td>59</td>
</tr>
<tr>
<td>66</td>
<td>1.210</td>
<td>54</td>
</tr>
<tr>
<td>Rhodamine B base std</td>
<td>2.255</td>
<td>100%</td>
</tr>
</tbody>
</table>
Figure 82. UV-Vis spectrum showing the absorption of rhodamine B base into the hydrogel matrix hydrogel formed by compound 11 at varying time points. The hydrogel was formed by adding 10 mg of compound 11 in 2.0 mL water. After the formation of the gel, 2.0 mL solution of rhodamine B base dye (0.02 mM) was added on top of the gel.
Figure 83. Gel pictures showing the absorption of rhodamine B base at different times.

All compounds were characterized using $^1$H NMR, $^{13}$C NMR, LCMS and melting point. The $^1$H NMR, $^{13}$C NMR and LCMS spectra of some selected compounds are shown in Figures 84 and 85 respectively.
Compound 17
Figure 84. (A) $^1$H NMR; (B) $^{13}$C NMR and (C) LCMS spectra of compound 17.

Compound 27
Figure 85. (A) $^1$H NMR; (B) $^{13}$C NMR and (C) LCMS spectra of compound 27.
4.3. CONCLUSIONS

We have synthesized and characterized a series of urea and amide derivatives in good yields from the head group, 12 which was derived from glucosamine. Some of the compounds were found to be effective low molecular gelators for organic solvents or aqueous solution. Although none of the compound formed gel in hexane, a good number of them formed gel in aqueous solution. The urea derivatives formed effective gelators at low concentration in a mixture of DMSO and water when compared to the amide derivative. This may be due to the extra hydrogen bonding in the urea derivatives. Rheology analysis also showed that the urea derivative is a better elastic gel than the amide derivative as compound 28 has a storage modulus of more 10,000. The potential application of the hydrogel formed by compound 11 was also studied. The gel was observed to release about 94% of the trapped naproxen drug after 7 hours. The gel formed by compound 11 also has application for waste cleaning as it was able to absorb 46% of rhodamine B base from the aqueous solution.

4.4. EXPERIMENTAL SECTION

**General Experimental Procedures:** All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen unless otherwise indicated. Air and moisture-sensitive reagents were handled under nitrogen conditions. Chromatography was carried out using silica 230-400 mesh silica gel mixed as a slurry with the eluent and columns were packed, rinsed, and run under air pressure. Analytical thin-layer chromatography (TLC) was performed on a pre-coated alumina silica gel. Visualization was either by short wave (254 nm) ultraviolet light, or by staining with phosphomolybdic acid (PMA) followed by brief heating on a hot plate or by a heat gun.
**Instrumentation:** $^1$H NMR and $^{13}$C NMR were recorded on a Bruker 400 MHz (100 MHz respectively for $^{13}$C). Spectra were referenced using CDCl$_3$ as solvents with the residual solvent peak as the internal standard ($^1$H NMR: $\delta$ 7.26 ppm, $^{13}$C NMR: $\delta$ 77.00 ppm for CDCl$_3$. Chemical shifts were reported in parts per million and multiplicities are as indicated: s (singlet), d (doublet), t (triplet), m (multiplet), br (broad) and dd (doublet of a doublet). Coupling constants, $J$, are reported in Hertz and integration is provided, along with assignments, as indicated. Low-resolution Mass Spectrometry were performed in the Department of Chemistry at Old Dominion University. Melting points were recorded using Stuart Automatic Mel-Temp® capillary melting point apparatus. UV-Vis analysis were performed using Varian 5000 UV-Vis-NIR spectrophotometer.

**Materials and methods.** Benzaldehyde dimethyl acetal (Alfa Aesar), N-Acetyl glucosamine (AK Scientific inc), hexanoyl chloride, benzoyl chloride, pyridine, ammonium chloride, succinic anhydride, 1-pyrenebutyric acid, bromoacetic anhydride, 3-chloro propanoic acid, Propanoic acid, pentyl isocyanate, hexyl isocyanate, heptyl isocyanate, phenyl isocyanate, benzyl isocyanate and cyclohexyl isocyanate. Solvents and reagents were obtained commercially and used directly without any further purifications. Solvents used for extraction and column chromatography were reagent grade and used as received. All the solvents used for the reaction were purchased from Sigma-Aldrich, VWR, and Fisher. Chromatography was carried out using silica 230-400 mesh silica gel. Thin-layer chromatography (TLC) analysis was performed with Sigma-Aldrich TLC plates, and visualized using UV lamp at 254 nm. $^1$H NMR and proton-decoupled $^{13}$C NMR spectra were obtained with Bruker 400 MHz spectrometers in CDCl$_3$. Proton and carbon spectra chemical shifts were reported using CDCl$_3$ as internal standard at 7.26 ppm and at 77.00 ppm respectively.
Gelation testing: In general, about 2 mg of the compounds were tested in a 1 dram vial with a rubber lined screw cap. To this vial, solvents were added in a 0.1 mL increment. A starting concentration of 20 mg/mL was used. The mixture was heated and sonicated until the sample was fully dissolved. The mixture was then allowed to cool at room temperature for 30 mins. The vial was then examined visually. If it appears as a homogenous semi-solid, the vial was then inverted; and if after being inverted, no solvent flows, then the gel is called a stable gel. If the semi-solid like material fell apart while being inverted, it is called an unstable gel. A serial dilution was performed on the stable gel formed until the resulting is no more stable. The concentration prior to the formation of the unstable gel was recorded as the minimum gelation concentration (MGC).

Rheological Analysis: The elasticity and stability of the gels were determined by doing rheological analysis. The rheology experiment was performed on a TA Instruments HR-2 Discovery hybrid rheometer, operating in oscillatory mode, with a 25 mm stainless steel parallel plate geometry. The Peltier temperature controller was set to maintain a temperature of 25 °C during the measurement. The gels were transferred to the center of the Peltier plate, the gel samples were analyzed immediately with a gap of 100 μm, and dynamic frequency sweep was performed from 0.1 to 100 rad/s with 5% strain.

Optical microscopy: A small amount of the stable gels was transferred to a clean glass slide using a spatula or pipette and was observed directly under an optical microscope. Some of the gels were left air dried for a few hours if too much liquid prevents imaging. The gels were observed using the 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 is the CellSens 1.11.
SYNTHESIS AND CHARACTERIZATION

Synthesis of compound 10. N-Acetyl glucosamine (2.0 g, 9.045 mmol) was dissolved in 15 mL of 1-butanol in a 100 mL round bottom flask. Amberlite resin, 2.0 g was rinsed with 5 mL of 1-butanol and filtered. The washed resin was then added into the reaction mixture and refluxed for 24 hours. The reaction was monitored using NMR. After completion of the reaction as confirmed by NMR, the reaction mixture was allowed to cool to rt and then filtered into a clean flask. The resin was washed several times with 1-butanol and the solution was added into the flask. The combined solution was concentrated under reduced pressure to obtain a crude yellow solid, 2.42 g, 96% yield. This crude product was used for the next step without any further purification.

Synthesis of compound 11. Compound 10 (2.42 g, 8.73 mmol, 1 equiv.) was dissolved in 8 mL of DMF. Benzaldehyde dimethyl acetal (1.58 mL, 10.5 mmol, 1.2 equiv.) was added followed by p-toluene sulfonic acid (150.3 mg, 0.873 mmol, 0.1 equiv). The mixture was heated at 65 °C for 12 h. NMR analysis shows complete conversion of the sugar starting material. The methanol by-product was removed under reduced pressure for 45 mins. The reaction mixture was then neutralized using NaHCO₃ (400 mg). The mixture was stirred at rt for 30 mins. The mixture was concentrated and then diluted using 40 mL x 2 DCM and washed with 20 mL water. The combined organic phase was dried using sodium sulphate, filtered and concentrated. The crude product was recrystallized using methanol and hexane mixture. The mother liquor was concentrated and purified by column chromatography using a solvent system of DCM:hexane:methanol. Obtained a while solid, mp 207.0-209.0 °C. Rf = 0.29, 5% MeOH/DCM. ¹H NMR (400 MHz, CDCl₃) δ 7.51-7.49 (m, 2H), 7.37-7.35 (m, 3H), 5.83 (d, J = 8.7 Hz, 1H), 5.56 (s, 1H), 4.82 (d, J = 3.9 Hz, 1H), 4.28-4.19 (m, 2H), 3.91 (pseudo t, J = 9.5, 9.9 Hz, 1H), 3.84-3.69 (m, 3H), 3.58 (t, J = 9.1 Hz, 1H), 3.42 (ddd, J = 6.5, 9.8, 13.1 Hz, 1H), 2.05 (s, 3H), 1.64-1.57 (m, 2H), 1.43-1.37 (m, 2H),
0.96 (t, \( J = 7.4 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 171.3, 137.1, 129.1, 128.2, 126.3, 101.8, 97.7, 82.1, 70.6, 68.8, 68.0, 62.5, 54.1, 31.4, 23.3, 19.3, 13.8; LC-MS m/z [M + H]\(^+\) calcd for C\(_{19}\)H\(_{28}\)NO\(_6\), 366.18; found 366.2.

**Synthesis of compound 12.** Compound \( 11 \) (1.18 g) was dissolved in a 3M solution of NaOH in ethanol. The reaction mixture was refluxed for 36 h. TLC and NMR analysis show that the reaction was completed. The mixture was concentrated under reduced pressure. The crude product was dried with 30 mL x 2 DCM and washed with 20 mL water. The combined organic phase was dried using sodium sulphate, filtered and concentrated to obtain a yellow solid, 0.866, 85 % yield, mp 112.0-114.0 °C. \( R_f = 0.2, \) 5% MeOH/DCM. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.51-7.49 (m, 2H), 7.38-7.35 (m, 3H), 5.53 (s, 1H), 4.76 (d, \( J = 3.3 \) Hz, 1H), 4.25 (dd, \( J = 4.6, \) 9.9 Hz, 1H), 3.82 (ddd, \( J = 4.7, \) 10.1, 14.1 Hz, 1H), 3.75-3.69 (m, 3H), 3.48-3.39 (m, 2H), 2.77 (d, \( J = 6.7 \) Hz, 1H), 1.63-1.56 (m, 2H), 1.45-1.36 (m, 2H), 0.94 (t, \( J = 7.4 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 137.3, 129.2, 128.3, 126.3, 101.9, 100.2, 82.2, 71.9, 69.2, 68.1, 62.7, 56.7, 31.6, 19.4, 13.9; LC-MS m/z [M + H]\(^+\) calcd for C\(_{17}\)H\(_{26}\)NO\(_5\), 324.2; found 324.2.

**Synthesis of compound 14.** Compound \( 12 \) (50 mg, 0.155 mmol, 1 equiv) was dissolved in 2.0 mL of DCM. Pyridine (38 \( \mu \)L, 0.463 mmol, 3 equiv) was added and the mixture was stirred in ice bath for 15 mins. Propanoic chloride (1.2 equiv) prepared in-situ from the acid derivative was added drop-wise into the reaction mixture in an ice bath. The reaction was stirred at 0 °C for 1 h and then at rt for 6 h. Reaction was monitored using TLC and NMR. After the consumption of the sugar starting material as confirmed by TLC and NMR, the reaction was stopped. Reaction mixture was diluted with 20 mL DCM and washed with 15 mL sat. ammonium chloride, water and brine respectively. The organic phase was then dried over sodium sulphate. The crude product was
concentrated under reduced pressure. The crude product was purified by column chromatography using a solvent mixture of ethyl acetate: hexane and the polarity was increased gradually to optimize the separation. The pure product was obtained as a white solid, 47.2 mg, 80% yield, mp 188.0-190.0 °C. Rf = 0.3, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52-7.49 (m, 2H), 7.39-7.34 (m, 3H), 5.83 (d, $J = 8.4$ Hz, 1H), 5.57 (s, 1H), 4.82 (d, $J = 3.9$ Hz, 1H), 4.28-4.19 (m, 2H), 3.91 (pseudo t, $J = 9.2$, 9.9 Hz, 1H), 3.82-3.69 (m, 3H), 3.59 (t, $J = 9.1$ Hz, 1H), 3.45-3.39 (m, 1H), 2.31 (dd, $J = 2.7$, 7.6 Hz, 1H), 2.27 (dd, $J = 2.7$, 7.6 Hz, 1H), 1.62-1.57 (m, 2H), 1.43-1.37 (m, 2H), 1.18 (t, $J = 7.6$ Hz, 3H), 0.95 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 175.1, 137.1, 129.2, 128.3, 126.3, 101.9, 97.7, 82.2, 70.9, 68.9, 68.0, 62.5, 54.1, 53.8, 31.4, 29.6, 19.4, 13.8, 9.6; LC-MS m/z [M + H]$^+$ calcd for C$_{20}$H$_{30}$NO$_6$, 380.2; found 380.2.

**Synthesis of compound 15.** Compound 12 (50 mg, 0.155 mmol, 1 equiv) was dissolved in 1.5 mL of DCM. Pyridine (38 µL, 0.463 mmol, 3 equiv) was added and the mixture was stirred in ice bath for 15 mins. A solution of hexanoyl chloride (26 µL, 0.186 mmol, 1.2 equiv) in 1.5 mL DCM was added drop-wise into the reaction mixture in ice bath. The reaction was stirred at 0 °C for 1 h and then at rt for 6 h. Reaction was monitored using TLC and NMR. After the consumption of the sugar starting material as confirmed by TLC and NMR, the reaction was stopped. Reaction mixture was diluted with 20 mL DCM and washed with 15 mL sat. ammonium chloride, water and brine respectively. The organic phase was then dried over sodium sulphate. The crude product was concentrated under reduced pressure. The crude product was purified by column chromatography using a solvent mixture of DCM:hexane:methanol and the polarity was increased gradually to optimize the separation. The pure product was obtained as a white solid, 46.4 mg, 71% yield, mp 196.0-198.0 °C. Rf = 0.5, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52-7.49 (m, 2H), 7.38-7.34 (m, 3H), 5.82 (d, $J = 8.5$ Hz, 1H), 5.57 (s, 1H), 4.82 (d, $J = 3.9$ Hz, 1H), 4.29-4.19 (m, 2H), 3.91 (pseudo t, $J = 9.2$, 9.9 Hz, 1H), 3.82-3.69 (m, 3H), 3.59 (t, $J = 9.1$ Hz, 1H), 3.45-3.39 (m, 1H), 2.31 (dd, $J = 2.7$, 7.6 Hz, 1H), 2.27 (dd, $J = 2.7$, 7.6 Hz, 1H), 1.62-1.57 (m, 2H), 1.43-1.37 (m, 2H), 1.18 (t, $J = 7.6$ Hz, 3H), 0.95 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 175.1, 137.1, 129.2, 128.3, 126.3, 101.9, 97.7, 82.2, 70.9, 68.9, 68.0, 62.5, 54.1, 53.8, 31.4, 29.6, 19.4, 13.8, 9.6; LC-MS m/z [M + H]$^+$ calcd for C$_{20}$H$_{30}$NO$_6$, 380.2; found 380.2.
2H), 3.92 (t, J = 9.9 Hz, 1H), 3.82-3.69 (m, 3H), 3.59 (t, J = 9.1 Hz, 1H), 3.42 (ddd, J = 6.5, 9.8, 13.1 Hz, 1H), 2.27-2.23 (m, 2H), 1.67-1.57 (m, 4H), 1.43-1.37 (m, 2H), 1.34-1.31 (m, 4H), 0.96 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 174.5, 137.1, 129.1, 128.3, 126.3, 101.9, 97.7, 82.2, 70.9, 68.9, 68.0, 62.4, 54.1, 36.7, 31.4, 31.3, 25.3, 22.4, 19.4, 13.9, 13.8; LC-MS m/z [M + H]+ calcd for C23H36NO6, 422.3; found 422.3.

**Synthesis of compound 16.** Compound 12 (75 mg, 0.232 mmol, 1 equiv) was dissolved in 3.0 mL of DCM. Pyridine (56 µL, 0.696 mmol, 3 equiv) was added and the mixture was stirred in ice bath for 15 mins. 4-pentynoic chloride (1.2 equiv) prepared in-situ from the acid derivative was added drop wise into the reaction mixture in ice bath. The reaction was stirred at 0 °C for 1 h and then at rt for 6 h. Reaction was monitored using TLC and NMR. After the consumption of the sugar starting material as confirmed by TLC and NMR, the reaction was stopped. Reaction mixture was diluted with 20 mL DCM and washed with 15 mL sat. ammonium chloride, water and brine respectively. The organic phase was then dried over sodium sulphate. The crude product was concentrated under reduced pressure. The crude product was purified by column chromatography using a solvent mixture of DCM:hexane:methanol and the polarity was increased gradually to optimize the separation. The pure product was obtained as a white solid, 68.4 mg, 70% yield, mp 185.0-186.0 °C. Rf = 0.4, 5% MeOH/DCM. 1H NMR (400 MHz, CDCl3) δ 7.51-7.49 (m, 2H), 7.38-7.35 (m, 3H), 6.01 (d, J = 8.5 Hz, 1H), 5.57 (s, 1H), 4.82 (d, J = 3.8 Hz, 1H), 4.29-4.22 (m, 2H), 3.94 (t, J = 9.6 Hz, 1H), 3.85-3.80 (m, 1H), 3.79-3.69 (m, 2H), 3.60 (t, J = 9.0 Hz, 1H), 3.42 (ddd, J = 6.5, 9.7, 13.1 Hz, 1H), 2.57-2.53 (m, 2H), 2.50-2.45 (m, 2H), 2.01 (t, J = 2.4 Hz, 1H), 1.62-1.59 (m, 2H), 1.43-1.39 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ
Synthesis of compound 17. Compound 12 (50 mg, 0.155 mmol, 1 equiv) was dissolved in 1.5 mL of DCM. K$_2$CO$_3$ (64.1 mg, 0.463 mmol, 3 equiv) was added and the mixture was stirred in ice bath for 15 mins. Bromoacetic anhydride (42.3 mg, 0.163 mmol, 1.05 equiv) dissolved in 1.5 mL DCM was added drop wise to the solution. Reaction mixture was stirred in ice for an hour and then at rt for 3.5 h. Reaction was monitored using TLC and NMR. After the consumption of the sugar starting material as confirmed by TLC and NMR, the reaction was stopped. Reaction mixture was diluted with 20 mL x 2 DCM and washed with 15 mL water. The organic phase was then dried over sodium sulphate. The crude product was concentrated under reduced pressure. The crude product was purified by column chromatography using a solvent mixture of DCM:hexane:methanol and the polarity was increased gradually to optimize the separation. The pure product was obtained as a white solid, 58.2 mg, 85% yield, mp 225-227 °C. R$_f$ = 0.4, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.51-7.49 (m, 2H), 7.40-7.36 (m, 3H), 6.84 (d, $J$ = 8.8 Hz, 1H), 5.56 (s, 1H), 4.82 (d, $J$ = 3.8 Hz, 1H), 4.28 (dd, $J$ = 4.5, 9.9 Hz, 1H), 4.20 (ddd, $J$ = 3.9, 10.0, 13.7 Hz, 1H), 4.00-3.95 (m, 2H), 3.91-3.88 (m, 1H), 3.83 (dd, $J$ = 4.8, 9.6 Hz, 1H), 3.79-3.72 (m, 2H), 3.58 (t, $J$ = 9.2 Hz, 1H), 3.47-3.41 (m, 1H), 1.65-1.58 (m, 2H), 1.48-1.39 (m, 2H), 0.95 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.3, 136.0, 128.3, 127.3, 125.3, 101.0, 96.6, 81.0, 69.5, 67.9, 67.2, 61.5, 53.4, 30.4, 28.7, 28.1, 18.4, 12.8; LC-MS m/z [M + H]$^+$ calcd for C$_{22}$H$_{30}$NO$_6$, 404.2; found 404.2.

Synthesis of compound 18. Compound 12 (100 mg, 0.309 mmol, 1 equiv) was dissolved in 3 mL of DCM. K$_2$CO$_3$ (128.2 mg, 0.926 mmol, 3 equiv) was added and the mixture was stirred in ice
bath for 15 mins. 3-chloro propanoic chloride (1.2 equiv) prepared in-situ was added drop wise to
the reaction mixture. Reaction mixture was stirred in ice for an hour and then at rt for 4 h. Reaction
was monitored using TLC and NMR. After the consumption of the sugar starting material as
confirmed by TLC and NMR, the reaction was stopped. Reaction mixture was diluted with 20 mL
x 2 DCM and washed with 15 mL water. The organic phase was then dried over sodium sulphate.
The crude product was concentrated under reduced pressure. The crude product was purified by
column chromatography using a solvent mixture of DCM:hexane:methanol and the polarity was
increased gradually to optimize the separation. The pure product was obtained as a white solid,
101.4 mg, 79% yield, mp 202.0-204.0 °C. Rf = 0.4, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$)
$\delta$ 7.51-7.50 (m, 2H), 7.36 (broad, 3H), 5.97 (d, $J = 7.8$ Hz, 1H), 5.57 (s, 1H), 4.83 (d, $J = 3.1$ Hz,
1H), 4.28-4.26 (m, 2H), 3.94 (t, $J = 9.8$ Hz, 1H), 3.82-3.70 (m, 5H), 3.59 (t, $J = 8.7$ Hz, 1H), 3.44-
3.42 (m, 1H), 2.76-2.64 (m, 2H), 1.62-1.59 (m, 2H), 1.42-1.39 (m, 2H), 0.95 (t, $J = 7.0$ Hz, 3H);
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.5, 137.1, 129.2, 128.3, 126.3, 101.9, 97.7, 82.0, 70.5, 68.9,
62.5, 54.1, 40.0, 39.7, 31.5, 19.4, 13.8; LC-MS m/z [M + Na]$^+$ calcd for C$_{21}$H$_{30}$ClNO$_6$Na, 450.2;
found 450.2.

**Synthesis of compound 19.** Succinic anhydride (25.53 mg, 0.255 mmol, 1.1 equiv) was dissolved
in 3 mL THF and the mixture was cool in ice bath for 1 hour. A solution of compound 12 (75 mg,
0.232 mmol, 1 equiv) in 1.5 mL DCM was added into the reaction mixture. The reaction mixture
was stirred in ice for an hour. Reaction was monitored using TLC and NMR. After the consumption
of the sugar starting material as confirmed by TLC and NMR, the reaction was stopped. Reaction
mixture was diluted with 20 mL DCM and washed with 15 mL water. The organic phase was then
dried over sodium sulphate. The crude product was concentrated under reduced pressure to obtain
a yellow solid product. 88.4 mg, 90%. Mp decomposed on heating. $^1$H NMR (400 MHz, CDCl$_3$)
δ 7.50-7.48 (m, 2H), 7.34-7.32 (m, 3H), 6.28 (d, \( J = 8.9 \) Hz, 1H), 5.50 (s, 1H), 4.75 (d, \( J = 3.6 \) Hz, 1H), 4.24-4.17 (m, 2H), 3.91 (t, \( J = 9.7 \) Hz, 2H), 3.82-3.76 (m, 2H), 3.74-3.63 (m, 3H), 3.56 (t, \( J = 9.1 \) Hz, 1H), 3.41-3.36 (m, 1H), 2.74-2.67 (m, 1H), 2.53-2.48 (m, 2H), 2.37-2.33 (m, 1H), 1.61-1.54 (m, 2H), 1.43-1.33 (m, 2H), 0.95 (t, \( J = 7.4 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 176.4, 173.7, 137.3, 129.0, 128.2, 126.3, 101.7, 97.9, 81.7, 70.0, 68.9, 68.1, 62.8, 54.1, 31.1, 31.2, 30.0, 19.3, 13.4; LC-MS m/z [M + H]\(^{+}\) calcd for C\(_{21}\)H\(_{30}\)NO\(_8\), 424.2; found 424.2.

**Synthesis of compound 20.** Compound 12 (50 mg, 0.155 mmol, 1 equiv) was dissolved in 1.5 mL of DCM. Pyridine (38 µL, 0.463 mmol, 3 equiv) was added and the mixture was stirred in ice bath for 15 mins. A solution of benzoic chloride (20 µL, 0.186 mmol, 1.2 equiv) in 1.5 mL DCM was added drop wise into the reaction mixture in ice bath. The reaction was stirred at 0 °C for 1 hr and then at rt for 6 h. Reaction was monitored using TLC and NMR. After the consumption of the sugar starting material as confirmed by TLC and NMR, the reaction was stopped. Reaction mixture was diluted with 20 mL DCM and washed with 15 mL sat. ammonium chloride, water and brine respectively. The organic phase was then dried over sodium sulphate. The crude product was concentrated under reduced pressure. The crude product was purified by column chromatography using a solvent mixture of DCM:hexane:methanol and the polarity was increased gradually to optimize the separation. The pure product was obtained as a white solid, 62.5 mg, 95% yield, mp 190.0-191.0 °C. \( R_f = 0.5, \) 5% MeOH/DCM. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.81-7.79 (m, 2H), 7.54-7.46 (m, 5H), 7.38-7.36 (m, 3H), 6.54 (d, \( J = 8.5 \) Hz, 1H), 5.60 (s, 1H), 4.94 (d, \( J = 3.9 \) Hz, 1H), 4.44 (ddd, \( J = 3.9, 9.9, 13.6 \) Hz, 1H), 4.30 (dd, \( J = 4.6, 9.8 \) Hz, 1H), 4.05 (t, \( J = 9.6 \) Hz, 1H), 3.91-3.74 (m, 3H), 3.67 (t, \( J = 9.1 \) Hz, 1H), 3.49-3.44 (m, 1H), 1.65-1.59 (m, 2H), 1.45-1.39 (m, 2H), 0.95 (t, \( J = 7.4 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 167.4, 136.1, 132.7, 131.0, 128.2,
Synthesis of compound 21. Compound 12 (50 mg, 0.155 mmol, 1 equiv) was dissolved in 2.2 mL of DCM. Pyridine (38 µL, 0.463 mmol, 3 equiv) was added and the mixture was stirred in ice bath for 15 mins. 1-pyrenebutyric chloride (1.2 equiv) prepared in situ from the acid derivative was added drop wise into the reaction mixture in ice bath. The reaction was stirred at 0 °C for 1 hr and then at rt for 6 h. Reaction was monitored using TLC and NMR. After the consumption of the sugar starting material as confirmed by TLC and NMR, the reaction was stopped. Reaction mixture was diluted with 20 mL DCM and washed with 15 mL sat. ammonium chloride, water and brine respectively. The organic phase was then dried over sodium sulphate. The crude product was concentrated under reduced pressure. The crude product was purified by column chromatography using a solvent mixture of ethyl acetate:hexane and the polarity was increased gradually to optimize the separation. The pure product was obtained as a brown solid, 30.9 mg, 33% yield, mp 188.0-189.0 °C. Rf = 0.5, 5% MeOH/DCM. 1H NMR (400 MHz, CDCl3) δ 8.30 (d, J = 9.3 Hz, 1H), 8.17 (d, J = 1.1 Hz, 1H), 8.14 (dd, J = 1.5, 12.4 Hz, 2H), 8.10 (s, 1H), 8.03 (s, 2H), 7.99 (t, J = 7.6 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.51-7.49 (m, 2H), 7.39-7.34 (m, 3H), 5.77 (d, J = 8.5 Hz, 1H), 5.56 (s, 1H), 4.78 (d, J = 3.9 Hz, 1H), 4.29-4.23 (m, 2H), 3.91 (t, J = 9.6 Hz, 2H), 3.80-3.73 (m, 2H), 3.68-3.57 (m, 2H), 3.45-3.38 (m, 2H), 3.36-3.30 (m, 1H), 2.37-2.34 (m, 2H), 2.29-2.22 (m, 2H), 1.55-1.48 (m, 2H), 1.33-1.26 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 174.0, 137.1, 135.6, 131.4, 130.9, 130.0, 129.2, 128.8, 128.3, 127.5, 127.3, 126.8, 126.3, 125.9, 125.0, 124.8, 123.3, 101.9, 97.7, 82.2, 70.9, 68.9, 68.0, 62.5, 54.1, 35.8, 32.5, 31.4, 29.7, 27.2, 19.3, 13.7; LC-MS m/z [M + H]+ calcd for C37H40NO6, 593.3; found 506.2.
Synthesis of compound 23. Compound 12 (75 mg, 0.232 mmol, 1 equiv) was dissolved in 4 mL THF and then pentyl isocyanate (0.025 mL, 0.232 mmol, 1 equiv) was added. Reaction mixture was stirred at rt for 4 h after which TLC shows complete conversion of the sugar starting material. Mixture was concentrated. The crude product was purified by flash chromatography using a solvent mixture of DCM:hexane:methanol. The product eluted from 1.1% methanol:DCM:hexane. Obtained a white solid, 84.6 mg, 83%, mp 187.0-188.0 °C. Rf = 0.4, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52-7.48 (m, 2H), 7.37-7.33 (m, 3H), 5.57 (s, 1H), 4.81 (d, $J = 3.4$ Hz, 1H), 4.79-4.74 (m, 2H), 4.28-4.25 (m, 1H), 3.93-3.87 (m, 2H), 3.84-3.75 (m, 2H), 3.74-3.68 (m, 1H), 3.58 (t, $J = 8.8$ Hz, 1H), (3.42 (ddd, $J = 6.5, 9.7, 13.0$ Hz, 1H), 3.18-3.12 (m, 2H), 1.64-1.56 (m, 2H), 1.54-1.46 (m, 2H), 1.42-1.36 (m, 2H), 1.34-1.28 (m, 4H), 0.95 (t, $J = 7.4$ Hz, 3H), 0.90 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.8, 137.2, 129.1, 128.2, 126.3, 101.9, 98.2, 82.2, 71.7, 68.9, 68.0, 62.4, 55.4, 40.8, 31.5, 29.7, 29.0, 22.4, 19.4, 14.0, 13.8; LC-MS m/z [M + H]$^+$ calcd for C$_{23}$H$_{37}$N$_2$O$_6$, 437.3; found 437.2.

Synthesis of compound 24. Compound 12 (75 mg, 0.232 mmol, 1 equiv) was dissolved in 4 mL THF and then hexyl isocyanate (0.038 mL, 0.232 mmol, 1 equiv) was added. Reaction mixture was stirred at rt for 12 h after which TLC shows complete conversion of the sugar starting material. Mixture was concentrated. The crude product was purified by flash chromatography using a solvent mixture of DCM:hexane:methanol. The product eluted from 1.3% methanol:DCM:hexane. Obtained a white solid, 95.2 mg, 91%, mp 179.0-180.0°C. Rf = 0.5, 5% MeOH/DCM. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.51-7.49 (m, 2H), 7.38-7.34 (m, 3H), 5.56 (s, 1H), 4.82-4.81 (m, 3H), 4.26 (dd, $J = 3.5, 8.9$ Hz, 1H), 3.91-3.87 (m, 2H), 3.83-3.68 (m, 3H), 3.58 (t, $J = 8.5$ Hz, 1H), 3.42 (ddd, $J = 6.5, 9.7, 13.0$ Hz, 1H), 3.15 (broad, 2H), 1.63-1.56 (m, 2H), 1.50-1.44 (m, 2H), 1.42-1.33 (m,
2H), 1.30-1.26 (m, 6H), 0.94 (t, $J = 7.4$ Hz, 3H), 0.88 (t, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.8, 137.2, 129.1, 128.2, 126.3, 101.8, 98.2, 82.1, 71.7, 68.9, 68.0, 62.4, 55.4, 40.8, 31.5, 31.5, 30.0, 26.5, 22.5, 19.4, 14.0, 13.8; LC-MS m/z [M + H]$^+$ calcd for C$_{24}$H$_{39}$N$_2$O$_6$, 451.3; found 451.3.

**Synthesis of compound 25.** Compound 12 (75 mg, 0.232 mmol, 1 equiv) was dissolved in 4 mL THF and then heptyl isocyanate (0.030 mL, 0.232 mmol, 1 equiv) was added. Reaction mixture was stirred at rt for 12 h after which TLC shows complete conversion of the sugar starting material. Mixture was concentrated. The crude product was purified by flash chromatography using a solvent mixture of DCM:hexane:methanol. The product eluted from 1.3% methanol:DCM. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.51-7.49 (m, 2H), 7.36-7.33 (m, 3H), 5.56 (s, 1H), 4.85 (d, $J = 7.6$ Hz, 1H), 4.81 (d, $J = 3.4$ Hz, 1H), 4.27-3.94 (m, 1H), 3.92-3.86 (m, 2H), 3.81-3.75 (m, 2H), 3.73-3.67 (m, 1H), 3.57 (t, $J = 8.7$ Hz, 1H), 3.42 (ddd, $J = 6.4$, 9.7, 13.0 Hz, 1H), 3.14-3.13 (m, 2H), 1.61-1.56 (m, 2H), 1.50-1.46 (m, 2H), 1.41-1.35 (m, 2H), 1.31-1.28 (m, 8H), 0.94 (t, $J = 7.4$ Hz, 3H), 0.88 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.9, 137.2, 129.1, 128.1, 126.3, 101.8, 98.2, 82.1, 71.6, 68.9, 68.0, 62.4, 55.4, 40.8, 31.7, 31.5, 30.0, 29.0, 26.8, 22.6, 19.4, 14.0, 13.8; LC-MS m/z [M + H]$^+$ calcd for C$_{25}$H$_{41}$N$_2$O$_6$, 465.3; found 465.3.

**Synthesis of compound 26.** Compound 12 (75 mg, 0.232 mmol, 1 equiv) was dissolved in 4 mL THF and then cyclohexyl isocyanate (0.039 mL, 0.232 mmol, 1 equiv) was added. Reaction mixture was stirred at rt for 12 h after which TLC shows complete conversion of the sugar starting material. Mixture was concentrated. The crude product was purified by flash chromatography using a solvent mixture of DCM:hexane:methanol. The product eluted from 1.0%
methanol:DCM:hexane. Obtained a light yellow solid, 94.3 mg, 91%, mp 234.0-235.0 °C. Rf = 0.4, 5% MeOH/DCM. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.52-7.49 (m, 2H), 7.38-7.34 (m, 3H), 5.57 (s, 1H), 4.81 (m, 2H), 4.28-4.24 (m, 1H), 3.91-3.87 (m, 2H), 3.81-3.68 (m, 3H), 3.60-3.55 (m, 1H), 3.51-3.46 (m, 1H), 3.42 (ddd, \(J = 6.7, 9.7, 13.0\) Hz, 1H), 2.56 (broad, 2H), 1.95-1.91 (m, 2H), 1.73-1.67 (m, 2H), 1.64-1.57 (m, 3H), 1.42-1.30 (m, 4H), 1.17-1.11 (m, 2H), 0.95 (t, \(J = 7.4\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 158.2, 137.2, 129.1, 128.2, 126.3, 101.8, 98.1, 82.1, 71.8, 68.9, 68.0, 62.3, 55.5, 49.5, 33.7, 33.6, 31.5, 25.5, 24.8, 19.4, 13.8; LC-MS m/z [M + H]\(^+\) calcd for \(\text{C}_{24}\text{H}_{37}\text{N}_{2}\text{O}_{6}\), 449.3; found 449.2.

**Synthesis of compound 27.** Compound 12 (75 mg, 0.232 mmol, 1 equiv) was dissolved in 4 mL THF and then phenyl isocyanate (0.030 mL, 0.232 mmol, 1 equiv) was added. Reaction mixture was stirred at rt for 12 h after which TLC shows complete conversion of the sugar starting material. Mixture was concentrated. The crude product was purified by flash chromatography using a solvent mixture of DCM:hexane:methanol. The product eluted from 1.3% methanol:DCM:hexane. Obtained a white solid, 88 mg, 86%, mp 248.0-249.0 °C. Rf = 0.4, 5% MeOH/DCM. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 8.67 (s, 1H), 7.48-7.45 (m, 2H), 7.40-7.37 (m, 5H), 7.25-7.21 (m, 2H), 6.92-6.88 (m, 1H), 6.04 (d, \(J = 8.8\) Hz, 1H), 5.63 (s, 1H), 5.30 (d, \(J = 5.6\) Hz, 1H), 4.81 (d, \(J = 3.6\) Hz, 1H), 4.17 (dd, \(J = 4.7, 9.8\) Hz, 1H), 3.81-3.74 (m, 2H), 3.70-3.62 (m, 2H), 3.61-3.51 (m, 2H), 3.44-3.37 (m, 2H), 1.59-1.53 (m, 2H), 1.44-1.37 (m, 2H), 0.90 (t, \(J = 7.3\) Hz, 3H); \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) 157.4, 139.8, 137.2, 128.3, 128.1, 127.4, 125.8, 120.5, 116.8, 100.2, 97.6, 81.3, 78.6, 67.8, 67.5, 66.5, 62.2, 53.8, 30.5, 18.2, 13.1; LC-MS m/z [M + H]\(^+\) calcd for \(\text{C}_{24}\text{H}_{31}\text{N}_{2}\text{O}_{6}\), 443.2; found 443.2.
Synthesis of compound 28. Compound 12 (75 mg, 0.232 mmol, 1.0 equiv) was dissolved in 4 mL THF and then benzyl isocyanate (0.038 mL, 0.232 mmol, 1.0 equiv) was added. Reaction mixture was stirred at rt for 12 h after which TLC shows complete conversion of the sugar starting material. Mixture was concentrated. The crude product was purified by flash chromatography using a solvent mixture of DCM:hexane:methanol. The product eluted from 1.0% methanol:DCM:hexane. Obtained a white solid, 97.4 mg, 92%, mp 217.0-218.0 °C. \( R_f = 0.5, 5\% \text{ MeOH/DCM} \). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \( \delta \) 7.47-7.44 (m, 2H), 7.40-7.36 9m, 2H), 7.33-7.30 (m, 2H), 7.27-7.21 (m, 3H), 6.59 (t, \( J = 5.9 \) Hz, 1H), 5.83 (d, \( J = 8.6 \) Hz, 1H), 5.62 (s, 1H), 5.20 (d, \( J = 5.4 \) Hz, 1H), 4.76 (d, \( J = 3.6 \) Hz, 1H), 4.28-4.22 (m, 2H), 4.15 (dd, \( J = 4.7, 9.5 \) Hz, 1H), 3.77-3.69 (m, 2H), 3.67-3.61 (m, 2H), 3.56-3.49 (m, 2H), 3.40-3.34 (m, 1H), 1.57-1.52 (m, 2H), 1.41-1.36 (m, 2H), 0.91 (t, \( J = 7.4 \) Hz, 3H); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)) \( \delta \) 157.4, 140.0, 137.2, 128.2, 127.6, 127.4, 126.4, 126.0, 125.8, 100.2, 97.7, 81.5, 67.9, 67.5, 66.5, 62.1, 54.3, 42.3, 30.5, 18.2, 13.1; LC-MS m/z [M + H]\(^+\) calcd for C\(_{25}\)H\(_{33}\)N\(_2\)O\(_6\), 457.2; found 457.2.
CHAPTER 5

CONCLUSION AND FUTURE RESEARCH

5.1 CONCLUSIONS

Different series of sugar based low molecular weight gelators (LMWGs) containing a triazole ring, an amide, urea and a light responsive group have been synthesized and characterized respectively. Moreover, the various potential applications of the gelators formed were analyzed including as drug delivery at varying pH solution and using UV light, dye absorption and in waste treatment. The sugar-based gelators were designed using N-acetyl glucosamine, maltose and lactose as starting materials. Disaccharide sugars, maltose and lactose were used for the design of triazole compounds in Chapter 2 as shown in Figure 86. N-acetyl glucosamine was used for the synthesis of various UV light and pH responsive sugar based gelators, amide and urea derivatives as shown in Figure 87 for Chapter 3 and Chapter 4.

![Figure 86](image_url)

**Figure 86.** Structure of lactose 1 and maltose 2 starting materials and the general structures of the lactosyl and maltosyl triazole derivatives (3 and 4).
Chapter 2 discussed the synthesis and design of sugar based low molecular weight gelators. This chapter focused on the synthesis and characterization of a series of peracetylated disaccharide triazole derivatives. The gelation abilities of the lactosyl and maltosyl triazole derivatives were tested in various solvents including water, IPA, toluene, hexane, ethanol and aqueous solutions. From the gel test results, the lactosyl triazole derivatives were observed to be poor gelators while the maltosyl triazole derivatives were effective gelators in most of the compounds tested. Figure 88 shows the structure of some of the compounds that formed effective low molecular weight gelators in various solvent including aqueous solutions. The shorter aliphatic chain derivatives 9 and 10 were effective gelator in all the aqueous solutions tested. The short chain alcohol derivative 11 did not form gel in any of the aqueous solution tested. However, compounds 12 and 13 with the long chain alcohol derivative and carboxylic acid derivative respectively were effective gelator in most of the aqueous solution tested. The difference in the gelation ability of compounds 11 and 12 was influenced by hydrophobic interaction. Compounds 14 and 15 containing the aromatic
substituents were effective gelators in ethanol and in all the aqueous solutions tested. The gelation ability of these compounds is influenced by hydrogen bonding and π-π interaction. The potential application of the gel formed by compound 13 was also studied for drug delivery. The gel formed by compound 13 was used in trapping sodium naproxen and chloramphenicol respectively and the drug was released gradually from the gel matrix at different rates depending on the pH of the solution on top of the gel. A higher amount of the drug was released to the aqueous phase at basic pH.

![Structures of different maltosyl triazole derivatives that are effective gelators.](image)

**Figure 88.** Structures of different maltosyl triazole derivatives that are effective gelators.

The synthesis and characterization of a novel series of sugar based light and pH responsive low molecular weight gelators were discussed in Chapter 3. Figure 89 shows the structure of some of the compounds that formed effective low molecular weight gelators. All the compounds in Figure 90 formed gel in the aqueous solution tested. In addition to their gelation abilities in aqueous solution, Compound 16 formed gel in toluene and IPA while 17 and 18 both formed gel in ethanol and IPA. The gelation abilities of these compounds can be attributed to hydrogen bonding, π-π
interaction and hydrophobic forces. The potential application of the gel formed by compound 17 was also studied for drug delivery.

![Structures of novel sugar based light and pH responsive gelators.](image)

**Figure 89.** Structures of novel sugar based light and pH responsive gelators.

Finally, chapter 4 focused on understanding the influence of anomeric substituent on gelation. Various amide and urea derivatives were synthesized and the gelation test results show that some of the derivatives are effective organogelators while only one amide was able to form a hydrogel. **Figure 90** shows the structure of some of the compounds that formed effective low molecular weight gelators in various solvent including water and aqueous solutions. For the amide series, both compounds 19 and 20 formed a hydrogel while compound 21 formed an effective gelator in a mixture of EtOH:H$_2$O (1:1). For the urea series, both compounds 22 and 23 were effective gelators in aqueous solutions including EtOH:H$_2$O (1:1) and DMSO:H$_2$O (1:1). The formation of the effective gelators by these compounds were attributed to the presence of hydrogen bonding.
and of $\pi$-$\pi$ interaction. Rheology analysis of the various gels formed also showed that the urea derivative was a better elastic gel than the amide derivative. The potential application of the hydrogel formed by compound 20 was also studied for its use in controlled release of naproxen sodium.

Figure 90. Structures of different amide and urea derivatives of N-acetyl glucosamine that are effective gelators

5.2 FUTURE RESEARCH

One of the challenges in the area of LMWGs is the difficulty in predicting if a given compound would be a good gelator as the structural requirement for effective gelation is still not well defined.
Hence, there is a continuous effort to screen numerous analogs of carbohydrate-based gelators in various solvents. Previous research in our group has shown that monosaccharide-based triazole derivatives from D-glucose and glucosamine are effective gelators. Further studies also showed that disaccharide-based triazole particularly, the maltose sugar are also effective gelators while the lactose-based gelators were observed to be poor gelators. Investigation of the gelation ability of another disaccharide-based triazole (sucrose) would be studied, as this would increase the scope of the molecular gelators. The future studies would also allow us to obtain structural features necessary for common disaccharide derivatives to function as LMWGs.

The application of carbohydrate-based gelators in oil spill treatment is an area of vital importance. The potential application of the gelator formed by compound 19 for oil waste treatment would be investigated further. The application of enzymes for the cleavage of the gelators (Chapter 3) for potential release of encapsulated drugs in the gel matrix would also be explored. The synthesis and application of effective carbohydrate-based photo-responsive gelators would be explored further. One of the challenges of using 2-nitrobenzyl derivatives as a photo-responsive group is its limited wavelength absorption. It absorbs in the UV region. However, the draw back to the use of UV light responsive supramolecules is their limited tissue penetration and the damage it causes to biological systems thereby limiting its application in the biomedical fields. Hence, UV responsive supramolecules only have potential applications to peripheral regions. Hence, to improve its application, the synthesis of visible light-responsive compounds that are responsive at a longer wavelength would be explored. Visible light responsive molecules have received great attention because of their intrinsic advantages including spatiotemporal precision and easy manipulation.
These longer wavelength (400-700 nm) visible light causes less damage to the tissue in comparison to UV light and hence makes it a viable alternative for light-activated drug delivery.
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**APPENDIX A**

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APPENDIX B

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Figure 1.

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Figure 2 and 3.
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