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# Design, Synthesis and Characterization of D-glucosamine Low Molecular Weight Gelators

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# Design, Synthesis and Characterization of D-glucosamine Low Molecular Weight Gelators

A Thesis

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Dedicated to:

My Family Members

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# Table of Contents

# List of Schemes

# List of Figures

# List of Tables

# Abstract

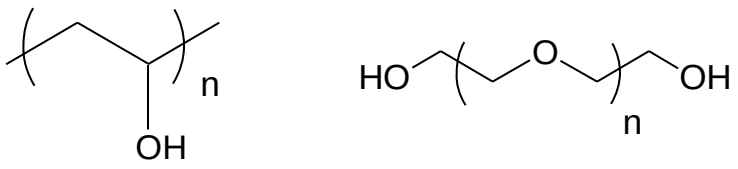
Low molecular weight gelators (LMWGs) have gained much attention over the last few decades, because of their ability to form supramolecular architectures as well as their many potential applications in biomedical research and as advanced materials. Most of the gelators were discovered through serendipity, and their structural requirements are somewhat ambiguous. This is due, in part, to the fact that the supramolecular gelation phenomenon is not yet fully understood, though many structural classes have been found to be excellent organogelators. Carbohydrates are abundant natural resources that are useful in preparing advanced materials. We have previously showed that monosaccharide derivatives can form effective low molecular weight gelators for both organic solvents and aqueous mixtures. In this research, we have studied the gelation capability of several glucosamine derivatives. Several series of 4,6-O-acetal protected glucosamine derivatives were synthesized and screened for their gelation properties in several solvents.



Keywords: Amides, Biomolecules, Enzymes, Solvents

# Introduction

The exact definition of a gel can be somewhat ambiguous. The word "gel" comes from Latin word "gelatus", which means to immobilize or to freeze. In general, a gel consists of two components: gelator molecules and solvent molecules; thus, a gel can be defined as a semisolid material in which a large amount of solvent molecules are entrapped within the three dimensional network formed by gelator molecules.[1-6] Several products that are used routinely in our everyday lives are comprised, at least in part, by gels; examples include contact lenses, shaving cream, shoe padding, etc. Gels have also shown many potential applications in biochemical fields, such as tissue engineering, drug delivery, and separation of RNA and DNA.[3,7] Most of the gels that we use in our routine life are polymer gels, in which covalent or chemical bonds are involved in the formation of the gel; hence, polymer gels are also known as chemical gels.[2-4] Polyvinyl alcohol **1** and polyethylene glycol **2** in Figure 1 are examples of polymers that form gels in water.

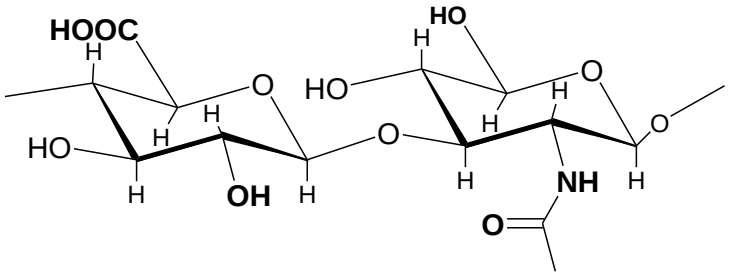



**1** **2**

**Figure 1.** Structures of two polymer hydrogels, polyvinyl alcohol **1** and polyethylene glycol **2**.

One major advantage of polymer gels is that they have good mechanical strength, but the gels are not degradable and typically require high concentrations of the polymer.[4] Several polymer gels have been used in various biochemical applications, such as tissue engineering; for example,

hyaluronate (Figure 2) is a naturally-occurring hydrogelator that has been used for growing artificial skin and intradermal implants, as well as for wound healing. [3]




**3**

**Figure 2.** Structure of hyaluronate, which has shown potential applications in tissue engineering.

Usually, gels are formed by dissolving the gelator in the solvent (water or organic solvent), using heat to help the compound dissolve, and then allowing the solution to cool. The temperature at which this solution forms a gel is known as the $T_{gel}$ (temperature of gelation).[8] Advantages of LMWGs include their ability to be synthesized from readily available, cheap starting materials, the ease of such syntheses compared to the syntheses of polymer gels, and that their formation is typically thermally reversible. Of particular significance is thermal reversibility, meaning that upon heating the gel, the gel goes back into solution (the temperature at which the gelator goes into the solution is known as the $T_{sol}$ temperature of solvation). [8, 9]

Gels formed by LMWGs are called physical or supramolecular gels, because of the fact that the formation of their three-dimensional networks occurs through non-covalent interactions, such as hydrogen bonding, hydrophobic interactions, π-π stacking, dipole-dipole interactions, and Van der Waals interactions. [8-12] Depending on the solvent in which they form a gel, LMWGS can be

divide into two types: hydrogelators (LMHGs) and organogelators (LMOGs). Different types of intermolecular interactions are important for LMHGs and LMOGs; hydrogelators depend mainly on hydrophobic interactions rather than hydrogen bonding for gel formation, while organogelators are primarily dependent on hydrogen bonding interactions.[10-12]

Low molecular weight gelators have found many applications in sensors, electrophotonics/photonics, cosmetics, hydrometallurgy, lubrications, structure directing agents (templates), conservation of art, etc.[13-20] Because the main driving force for supramolecular hydrogel is hydrophobic interactions, the structure of hydrogelators mainly consists of contrasting polar and nonpolar regions, in which polar groups mainly include amino acids or sugars,[20-29] while the nonpolar regions mainly include long alkyl chains or aromatic rings.[30-32] Figure **3** shows the structures of several compounds (**4**-**8**) that can form gels in water. Compounds **6** and **7** are ambidextrous (they are able to gelate both water and organic solvents).[33] Compound **8** has a unique bisoxalyl group with a phenyl side chain; it forms gels in organic solvents, and it was found that the *trans* isomer can also form a gel in water. [34]

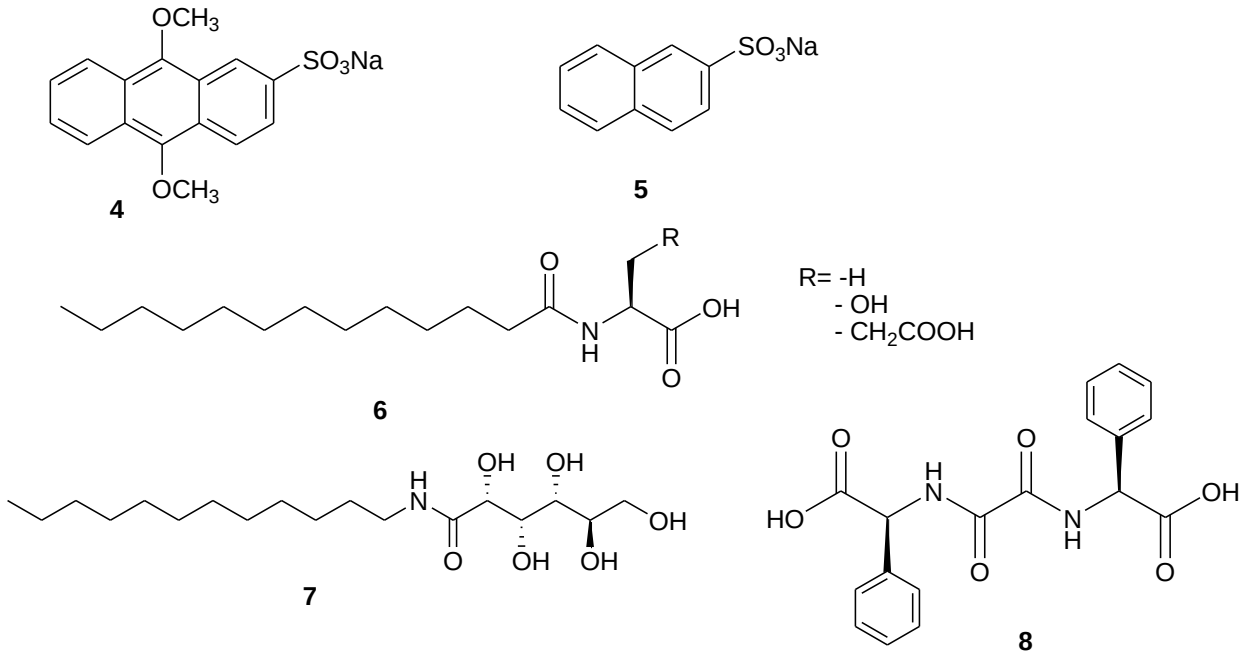



**Figure 3.** Structures of some hydrogelators.[32-34]

Many studies have been directed towards designing hydrogelators. Most of them are discovered serendipitously, and improved analogs are found by modifying the parent structure. To design a hydrogel, there must be a balance between the polar and nonpolar groups. Furhop and coworkers synthesized a library of LMHGs by introducing the alkyl amine chain into several aldonic acids.[33] Hamilton's group has shown that ureas with short alkyl chains act as hydrogelators, while those with larger chains act as organogelators.[25] Urea derivatives are placed in a separate category, because they exhibit strong hydrogen bonding, even in water.[25] Suzuki and their group synthesized many compounds with positively charged nitrogen atom into the structure and tested for their gelation activity, many of them form a good gel in pure water.[28] Figure **4** shows several hydrogelators that can form a gel at low concentrations (up to 1mg/mL).[28]

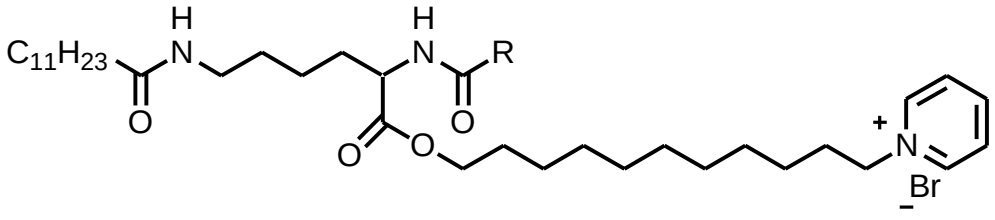



**Figure 4.** Structure of series of hydrogelators. [28]

The main attractive forces responsible for gel formation in organic solvents are hydrogen bonding, dipole-dipole interactions, and metal coordination. Weiss and Lin[35-37] employed a molecular engineering approach in their design of organogelators by investigating the influence of changing three structural components: aromatic groups, linkers, and steroids;

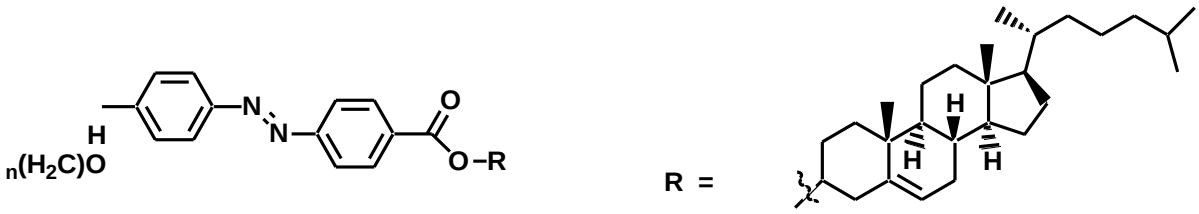



**Figure 5.** ALS Gelators[35-37]

They found that the shape of the molecules is vital, compound in figure **5** are more efficient gelator with their β anomers compared to their α anomers.[38] There are several organogelators are shown in Figure **6.** Compound **9** form a gel in various organic solvents such as alcohols, nitriles,

amines and alkanes but addition of alkoxy group at 2 and 3 positions loose their gelation activity Compound **11** form a lyotropic gels[41] While compound **13** can form gel in various polar organic solvents such as DMSO, DMF, 1,2 dichloroethane and nitrobenzene but replacing alkyl chain with shorter chain length reduces gelation efficiency.[42] LMOGs have been used in many industrial applications, such as lubrications and cosmetics, for a very long time. Currently, they have also shown many potential applications as sensors, electrophotonics/photonics, hydrometallurgic compounds, structure directing agents (templates), art conservation agents, etc.[13-20]

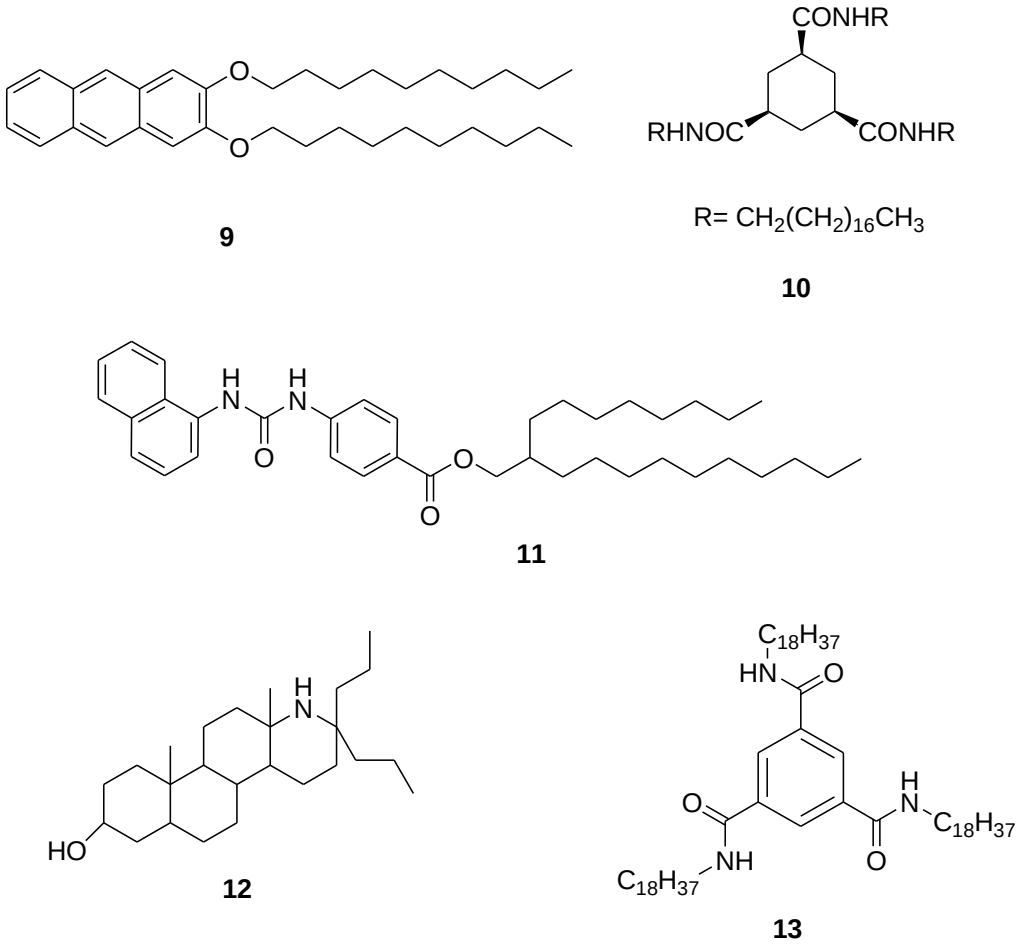



**Figure 6.** Structure of various LMOGs.[39-42]

Consideration of raw material is always necessary when designing a synthesis of drug molecule. It should be available readily with low cost. Various carbohydrate derivatives are naturally available and also some of them found in human body. They are biocompatible, and have no harmful effect if inserted into the human body. They also possess multiple free hydroxyl groups, which can aid in solubility, and be harnessed for their ability to form hydrogen bonds; the inherent chirality of these hydroxyl groups can also be used to direct the hydrogen bonds. There are a number of gelators that are derived from sugars; for example, Wang and coworkers[43-47] have synthesized many sugar based gelators that behave as hydrogelators as well as organogelators. Hydrogel formed by the sugars can be used in some biochemical applications.

Many drugs have some toxicity issues that can be reduced by reducing the concentration of the drug, but reducing the dose of drug also reduces the activity. This problem can be overcome by increasing the local concentration of drug at the target site. This can potentially be achieved by converting the drug into a prodrug analogue that is a hydrogelator. Bing Xu and their group has shown that by functionalizing Vancomycin with a pyrene group, hydrogelation can occur and it can be useful in sustained drug delivery.[46] While Tiller has shown that addition of pyrene moiety to Vancomycin leads to hydrogel formation, which can then be tethered on the cell surface, increasing the local concentration of the drug at the target site.[47] However, one must pay attention to the toxicity issues arising from the build up of undesirable byproducts formed by the degradation of the gelator molecules. Because sugars are ubiquitous in living organisms, the degradation products of the sugar based hydro gels are likely to be biocompatible. Figure **7** shows some sugar-based hydrogelators.

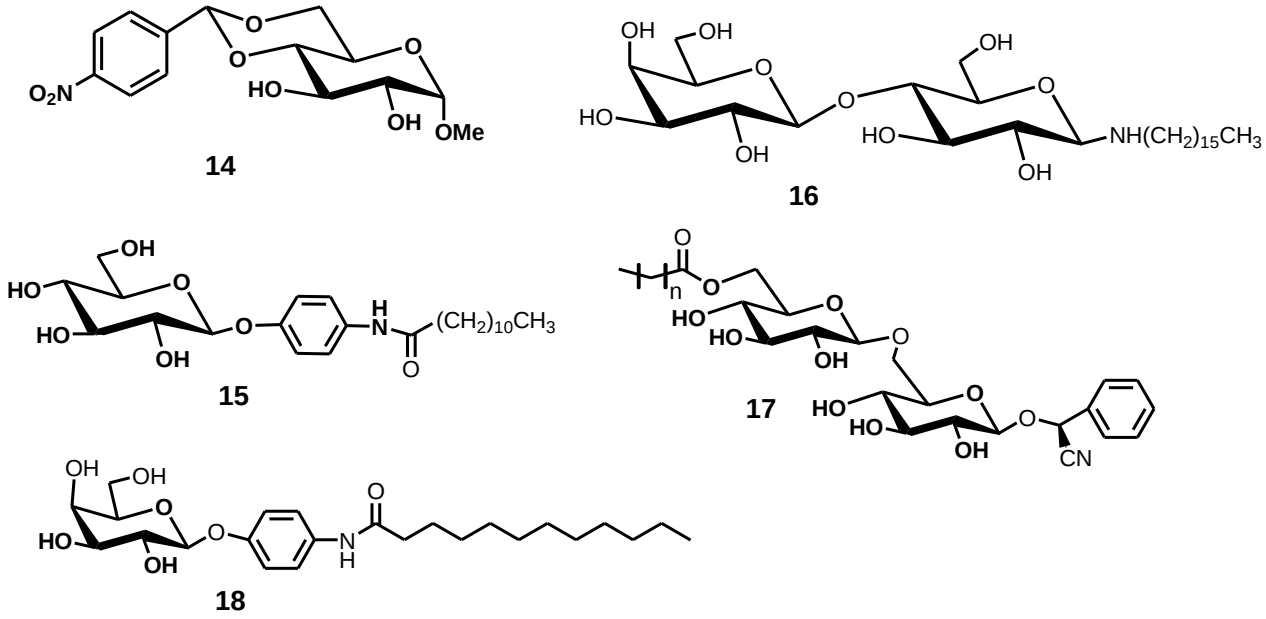



**Figure 7.** Several sugar-based hydrogelators. [48-51]

George John and his group have synthesized several amygdaline derivatives by incorporating long chain fatty acids to their structure. These compounds were tested for their gelation activity, and all of the derivatives showed good gelation activity in polar and nonpolar solvents. The gels were then tested for their proclivity for degradation in the presence of hydrolase and lipolase enzymes; it was found that degradation of the gel occurred by the cleavage of the ester bonds by the hydrolase enzyme, and that the long chain fatty acids were necessary for gelation. Shinkai and Hung have shown that compound **14** can form a gel in different organic solvents through intermolecular hydrogen bonding, and that the compound can also gel water through π-π stacking.[48] Shimizi's group has reported several aldopyranoside based amphiphilic gelators. This compound mostly forms a gel in organic solvents, but can also form a gel in water in presence of small amount of methanol or ethanol, which was necessary for solvation.[49-52]

**Our research:**

Our group has discovered several novel classes of organogelators and hydrogelators derived from common monosaccharides. We previously synthesized several aliphatic and aromatic ester derivatives of 4,6-O-benzylidene-methyl-α-D-glucopyranoside, and found that the compounds with short, terminal acetylene containing side chains (compounds **20**, **21**, and **22)** were good gelators. We also prepared some long chain (18-22 carbon) alkynyl esters derivatives that can gelate ethanol/water mixtures, and we found that the terminal alkynyl group is essential for the gelation activity.[43]

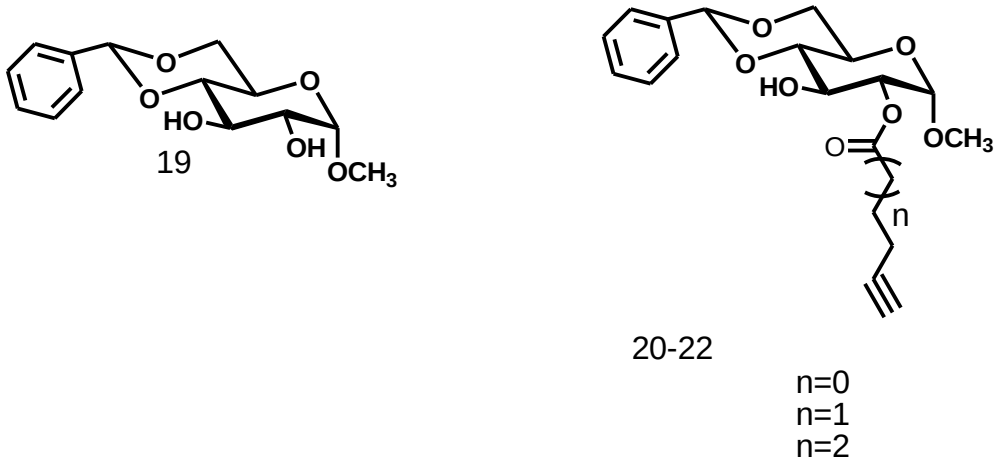



**Figure 8.** Sugar derived low molecular weight gelators.

In addition, our group has also synthesized several N-linked carbamates (in which the nitrogen atom is attached to the sugar head group) and O-linked carbamates (in which the oxygen atom is attached to the sugar head group) derivatives of the previous 4,6-O-benzylidene-methyl-α-D-glucopyranoside esters, and we have found that, unlike the ester derivatives, it is not necessary to have a terminal alkynyl group for good gelation activity. Compounds with the saturated alkyl

group and cyclohexyl group proved to be very good gelators.[45] The N-linked carbamate compounds **24** can form gels at concentrations as low as 1.7 mg/mL in DMSO:$H_2O$ (1:2), while in EtOH:$H_2O$ it can form gels at concentrations as low as 2.2 mg/mL. O-linked carbamate compounds **25** formed gels at concentrations as low as 1 mg/mL, in both DMSO:$H_2O$ and EtOH: H2O. [45]

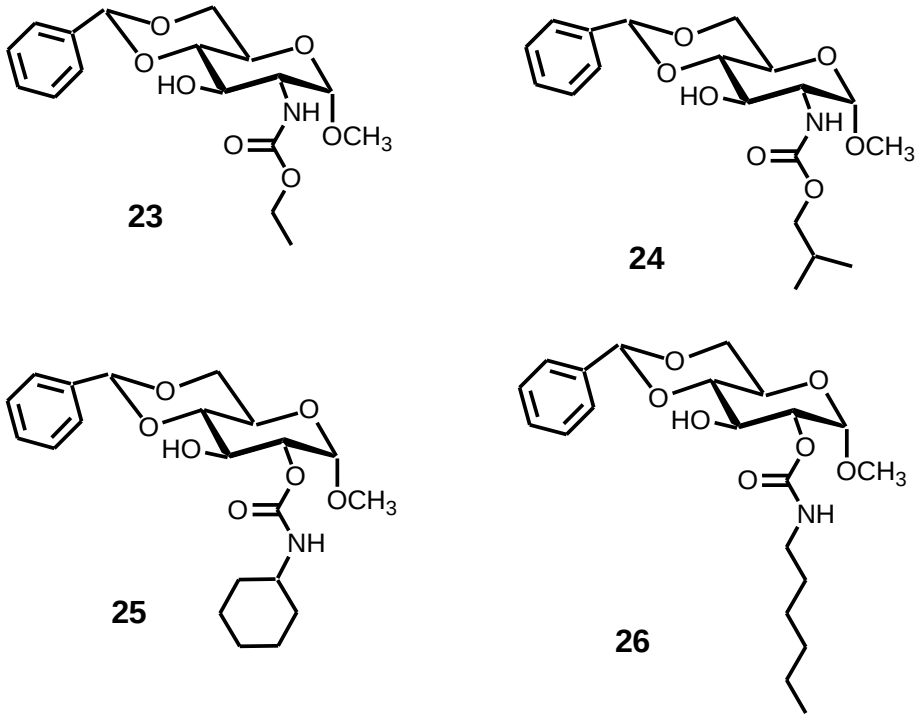


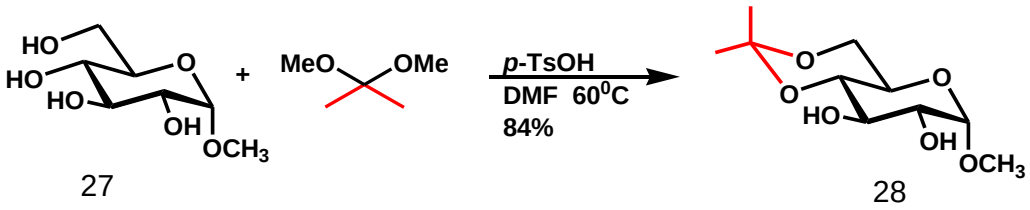

**Figure 9.** O-Linked and N-linked carbamates derivatives. [45]

We are interested in synthesizing and characterizing other sugar derivatives in order to better understand their self assembling behavior in different solvents, and to determine the role of the head group in gel formation. Thus, we synthesized other head groups derived from sugar molecules, made some ester and amide derivatives, and analyzed them for their gelation activity.

## Results and Discussions:

### 1. Synthesis and characterization of 4,6-O-isopropylidene acetal derivatives

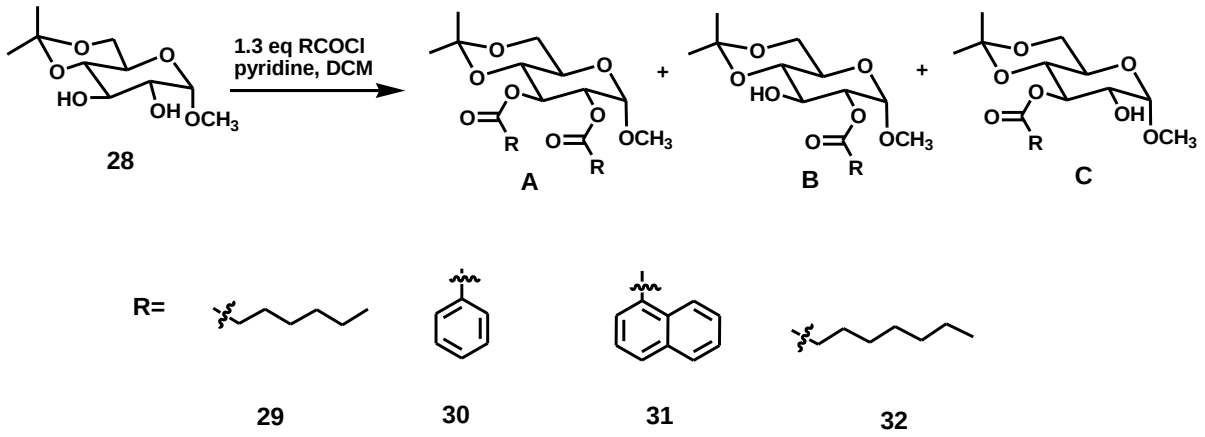
The preparation of the 4,6-O-isopropylidene-protected headgroup **28** is shown in Scheme 1. Compound **28** was synthesized from methyl-α-D-glucopyrinoside **27** by treating it with 2,2 dimethoxy propane in the presence of a catalytic amount of p-toluenesulphonic acid in anhydrous dimethylformamide (DMF). The reaction was run for 16 hrs at 70$^{o}$C. Product was purified by flash chromatography using Hexane: ethyl acetate as a solvent and gives 84% yield.




27 28

**Scheme 1.** Synthesis of 4,6-O isopropylidene acetal head group.

Once compound **28** was obtained, several esterification reactions using the corresponding acid chlorides were carried out to afford the 2,3-diesters **29-32A**, 2-esters **29-32B**, and 3-esters **29-32C** (Scheme 2). Generally compounds **A** and **B** were the major products; when the acyl group is less bulky, the 3-ester derivatives **C** were obtained in small quantities.




**Scheme 2.** Synthesis of isopropylidene ester derivatives.

The products were purified by flash chromatography using fine silica gel and hexane: ethyl acetate as the eluent. Once the compounds were purified and dried thoroughly under vacuum, their gelation properties were evaluated in several different solvents: hexane, ethanol, water, ethanol:water 1:2, and DMSO:water 1:2. To test the gelation, 2-4 mg of compound and 0.1mL of solvent were transferred into the testing vials and heated and sonicated until the compound was fully dissolved. The resulting solution was allowed to sit undisturbed for 20 minutes while it cooled back to room temperature. The compound was observed to see if precipitation, recrystallization, or gelation had occurred (or if the compound had remained solvated). If the compound had appeared to gelate (the mixture was homogenous and its viscosity had greatly increased), the sample vial was inverted; if the mixture didn't flow and stuck to the bottom of the vial, it was denoted as a stable gel, while unstable gels were denoted as mixtures in which some flow or escape of solvent from the matrix was observed. Compounds which formed a stable gel were further diluted by 0.1 mL of solvent to determine the minimum gelation concentration.

Table 1 shows the gel testing results of the various 2-ester derivatives (**29-32B**). Table 2 shows the gel testing results of various dimer derivatives (**29-32A**). Most of the isopropylidene ester derivatives were insoluble in hexane and water, and soluble in the remaining solvents.

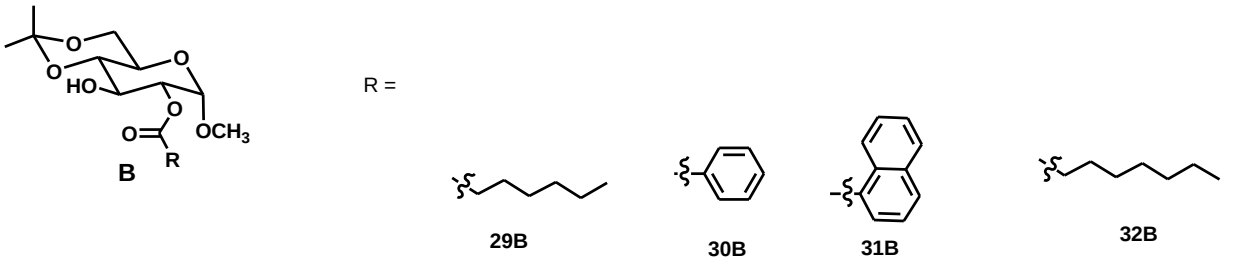
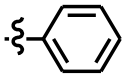
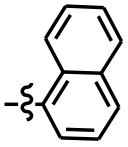
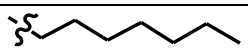



**Table 1.** Gelation Test results for 2-esters derivatives of 4,6-O isopropylidene derivatives. Positive gelation results are listed in mg/mL. * Unstable gel. I – insoluble, P – precipitate, S – soluble at 20 mg/mL

| Compound Number | R = | Hexane | Ethanol | Water | DMSO:$H_2O$ (1:2) | EtoH:$H_2O$ (1:2) |
|---|---|---|---|---|---|---|
| **29B** |  | I | S | I | S | S |
| **30B** |  | I | S | I | S | S |
| **31B** |  | I | S | I | S | S |
| **32B** |  | I | S | I | S | S |

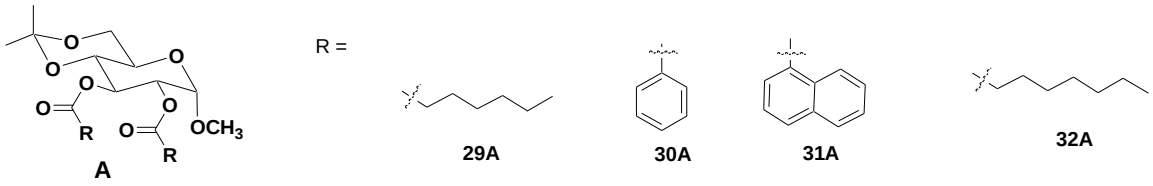
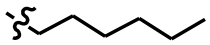
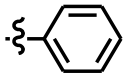
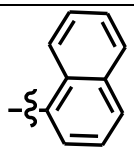
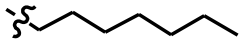



**Table: 2** Gelation test results for dimers of 4,6-O-isopropylidine acetal. Positive gelation results are listed in mg/mL. * Unstable gel. I – insoluble, P – precipitate, S – soluble at 20 mg/mL

| Compound Number | R= | Hexane | Ethanol | Water | DMSO:$H_2O$ (1:2) | EtoH:$H_2O$ (1:2) |
|---|---|---|---|---|---|---|
| **29A** |  | I | S | I | S | S |
| **30A** |  | I | S | I | S | S |
| **31A** |  | I | S | I | S | S |
| **32A** |  | I | S | I | S | S |

## 2. D-glucosamine derivatives

As we have seen, the ester derivatives of 4,6-O benzylidene-methyl-α-D-glucopyranoside with a free hydroxyl group at the 3-position form good gels in water and organic solvents, while the diester derivatives were less effective gelators.[43] In addition, isolation of the dimer and monoesters from one another proved to be challenging in some instances. D-glucosamine is another naturally occurring sugar found in many plants as well as in the human body. For

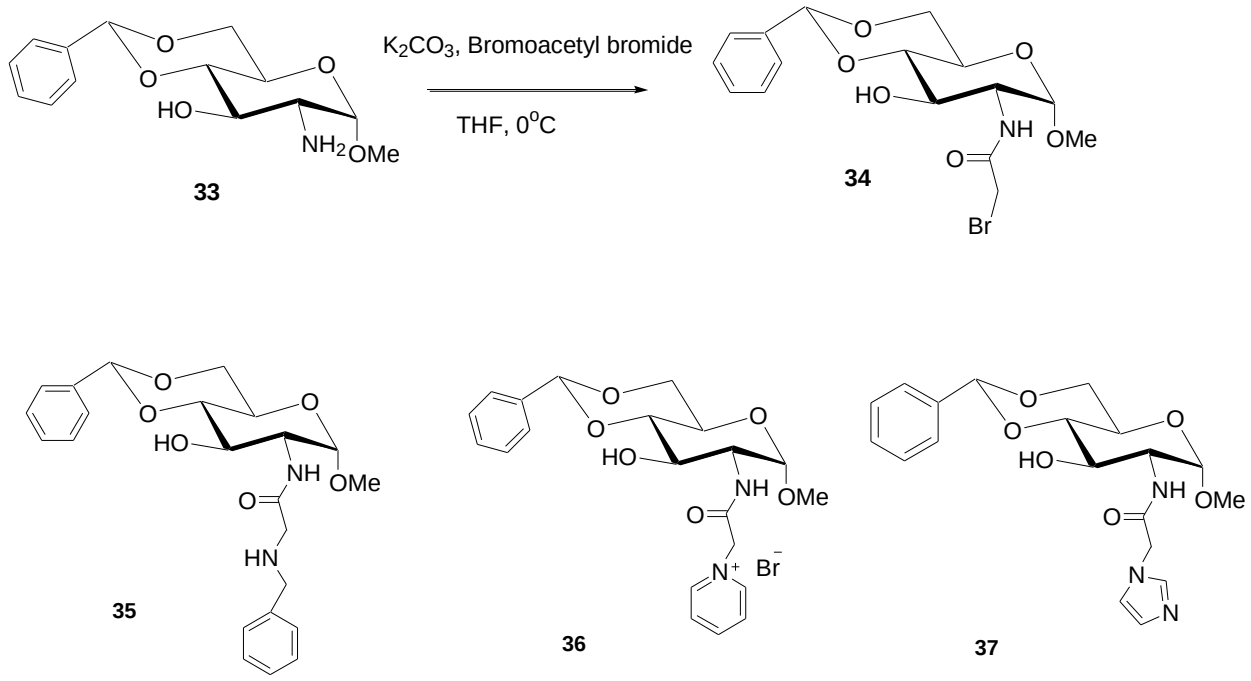
example, chitosan is the N-deacetylated product of chitin, and has found many applications in tissue engineering due to its biocompatibility and low toxicity.[3] Methyl pyrrolidinone derivatives have shown some positive effect on bone formation.[3] Hyaluronate is another glucosamine-based natural hydrogelators; several hydrazine derivatives of hyalluronate have been shown to form a hydrogel by covalent cross-linking.[3] Hydrogels formed by hyalluronate derivatives can be degraded in the presence of enzymes present in serum; as a result, there are potential applications for drug delivery, as well as in tissue engineering.[3]

From a synthetic view point, the amino group is more reactive than a hydroxyl group, and better regioselectivity should be exhibited, leading to easier separation and better yields. In addition, the formation of an amide may lead to increased gelation activity, as the hydrogen bonding of amides is stronger than esters, which might be helpful in the gelation mechanism; our previous research in this area has shown that the amides form better gels than the esters.

### 2.1. Preparation of cationic amide derivatives

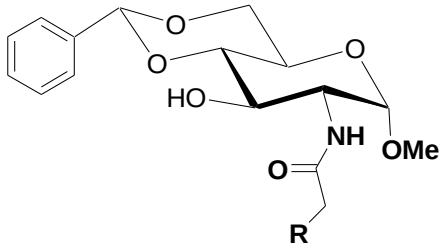
Our group has already synthesized several amides with the 4,6-O benzylidene acetal as the head group, and we have shown that most of the amides are good gelators in aqueous mixtures of ethanol and water or DMSO and water, but few of the amides form gels in pure water. We are interested in forming hydrogels, so we introduced a benzyl amine group or an imidazole group into the compounds in an effort to improve the solubility of the compounds in water. As shown in Scheme **3**, synthesis of the product was carried out by treating compound **33** with one equivalent of bromo acetyl bromide in presence of 2 equivalents of potassium carbonate for six hours. The product was purified by flash chromatography using a solvent gradient of

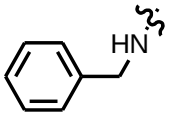
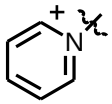
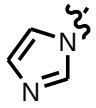
Hexane:DCM:MeOH as the eluent. The resulting product **34** was then reacted with 2 equivalents of benzyl amine, pyridine, or imidazole in DMF at 60°C for 12 hrs to form compounds **35**, **36**, **37**, respectively. These compounds were analyzed for their gelation activity, and the results are shown in Table 3.



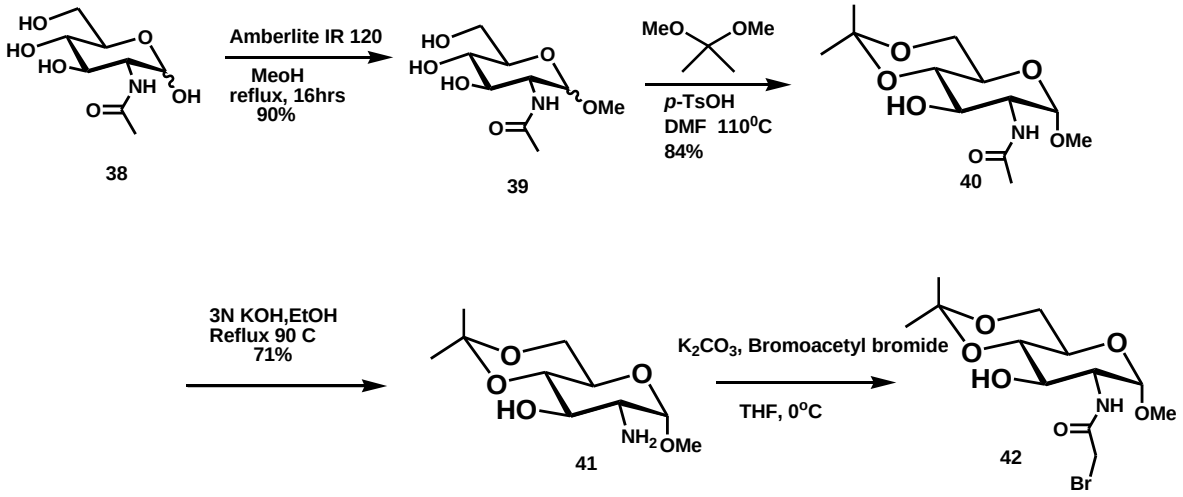

**Scheme 3.** Synthesis of amino-acetyl amide derivatives of **34**.

**Table: 3** Gelation Test results for compounds **35-37**. Positive gelation results are listed in mg/mL. Legend: *-Unstable gel, I – insoluble, P – precipitate, S – soluble at 20 mg/mL

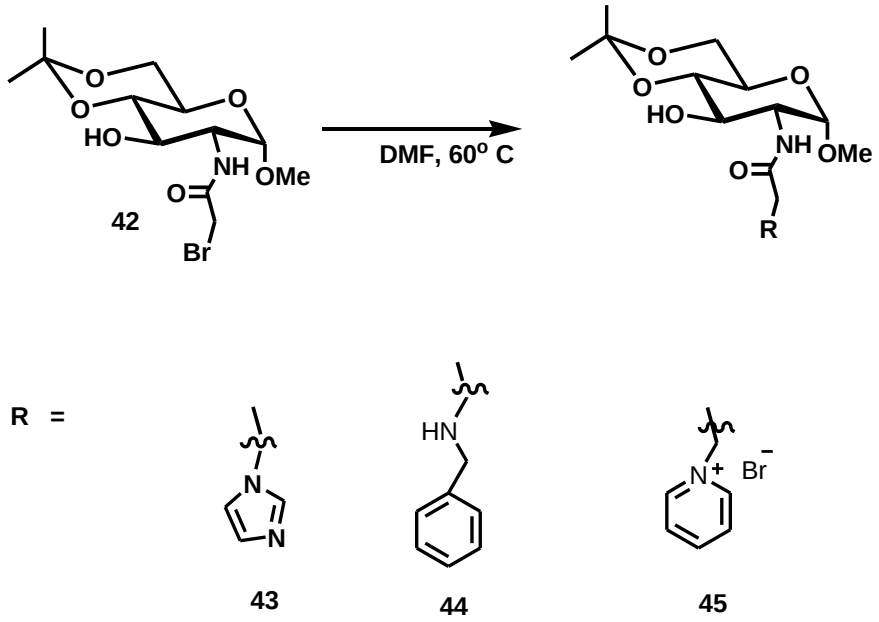



| Compound Number | R= | Hexane | Ethanol | Water | DMSO:$H_2O$ (1:2) | EtoH:$H_2O$ (1:2) |
|---|---|---|---|---|---|---|
| **35** |  | I | S | I | 6.0 | 5.7 |
| **36** |  | I | S | 10 | 5.0 | 5.0 |
| **37** |  | I | S | I | 7.0 | 7.0 |

Besides benzylidene acetal, we also prepared the derivatives with isopropylidene acetal for comparison purposes. These are shown in Schemes 4; the synthesis of **42** followed similar methods to those for the preparation of acetal **34**, using dimethoxypropane as the reagent instead of benzylidene dimethyl acetal.[45] Once product **42** was synthesized, it was reacted with 2 equivalents of benzyl amine, imidazole, or pyridine to afford compounds **43**, **44**, and **45**.



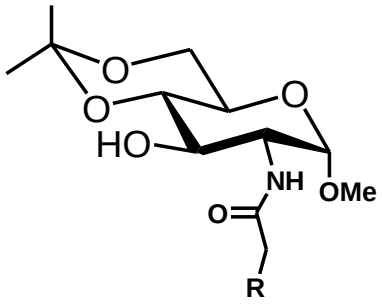

**Scheme 4.** Synthesis of isopropylidene protected glucosamine **42**.

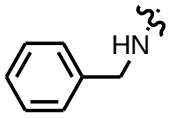
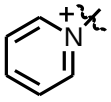
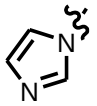



**Scheme 5.** Synthesis of isopropylidene protected heterocyclic derivatives of glucosamine.

The gelation test results are shown in Table 4. Compared to the benzylidene acetal derivatives **35-37**, compounds **43-45** are not effective gelators in the solvents tested. This indicated that the 4,6-benzylidene acetal protective group is important for gelation. To further test the tolerance of the acetal group, we then prepared p-methoxy benzylidene acetal derivatives as shown in the next section.

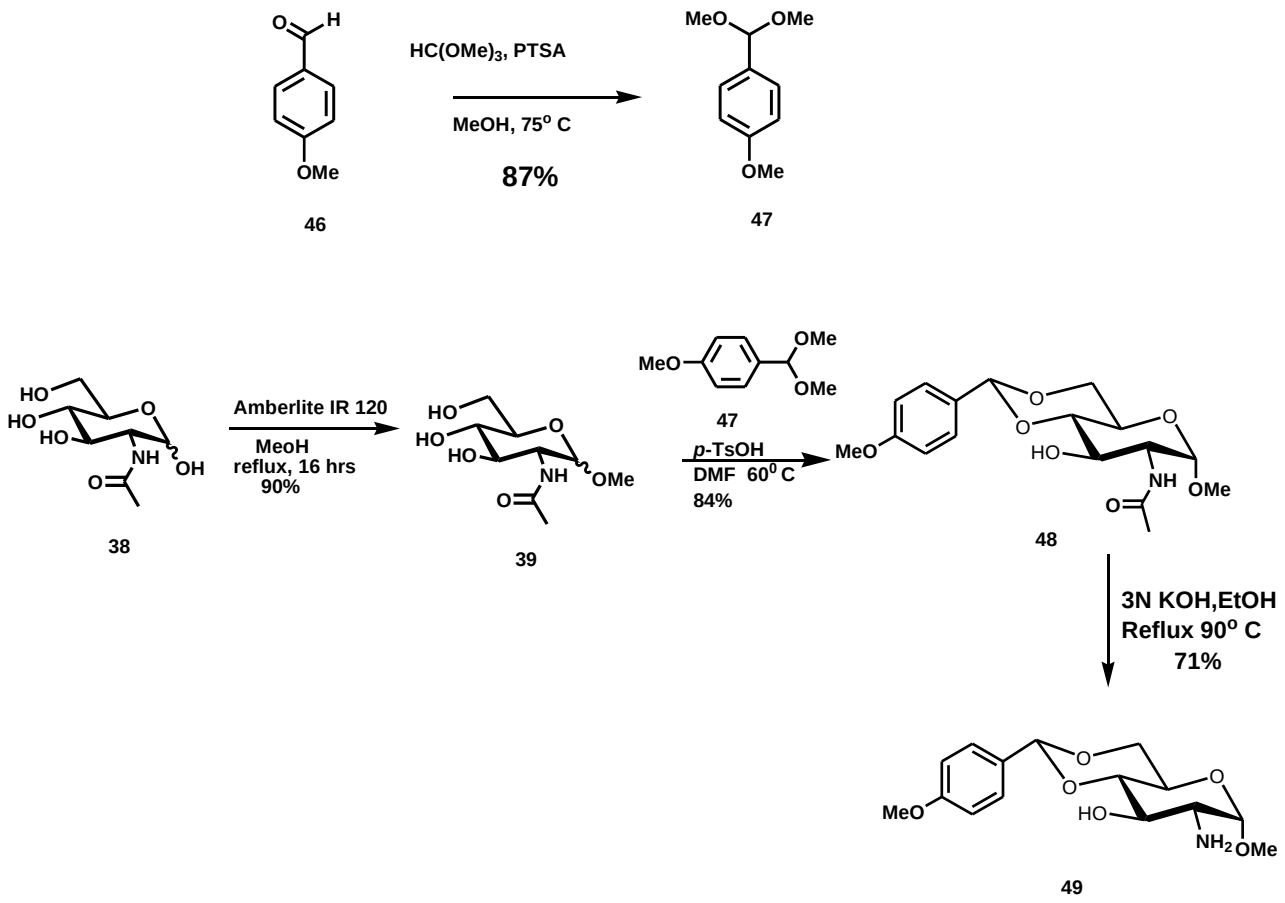
**Table 4:** Gelation test results for amide derivatives of 4,6-O-isopropylidine acetal derivatives. Positive gelation results are listed in mg/mL. Legend: *-unstable gel, I – insoluble, P – precipitate, S – soluble at 20 mg/mL.




| **Compound number** | R= | Hexane | Ethanol | Water | DMSO:$H_2O$ (1:2) | Ethanol:$H_2O$ (1:2) |
|---|---|---|---|---|---|---|
| **43** |  | I | S | I | S | S |
| **44** |  | I | S | S | S | S |
| **45** |  | I | S | S | S | S |

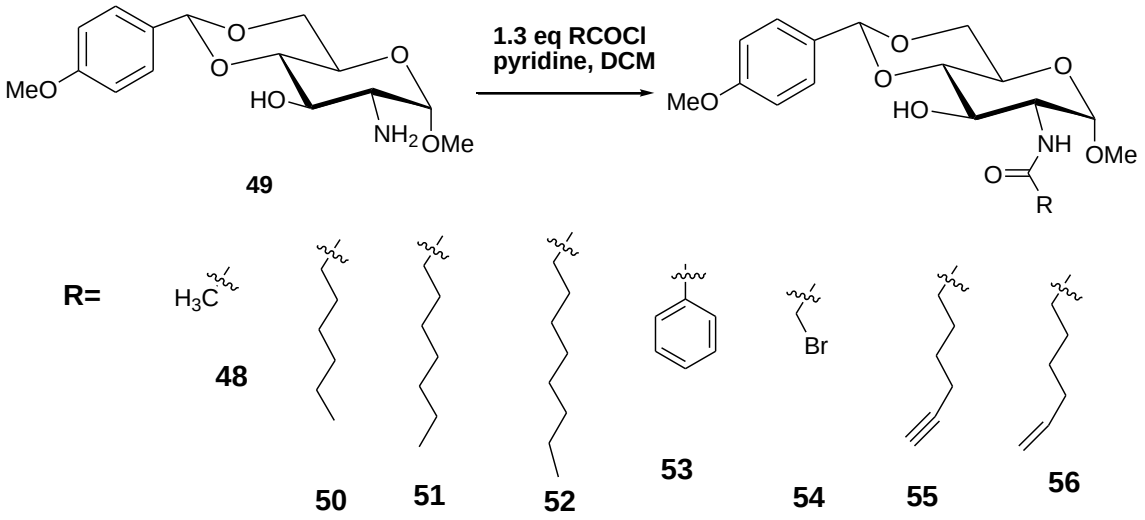
### 2.2. Synthesis of 4,6-O- p-methoxybenzylidene protected glucosamine derivatives

Synthesis of the p-methoxybenzylidene head group was relatively straight forward, as it was analogous to the synthesis of the benzylidene protected compound **40** (Scheme 5). In the first step, the anomeric hydroxyl group of *N*-acetyl-*D*-glucosamine was converted to a methoxy group by refluxing the compound in methanol in the presence of Amberlite IR-120 resin. After removal of the methanol and drying under vacuum, the resulting product was dissolved in anhydrous DMF, and reacted with compound **47** for 16 hrs in the presence of p-toluenesulfonic acid to give compound **48**. Deprotection of acetyl group was carried out with potassium hydroxide in ethanol for 16 hrs at reflux, and after workup, purification was conducted by column chromatography to give compound **49**.

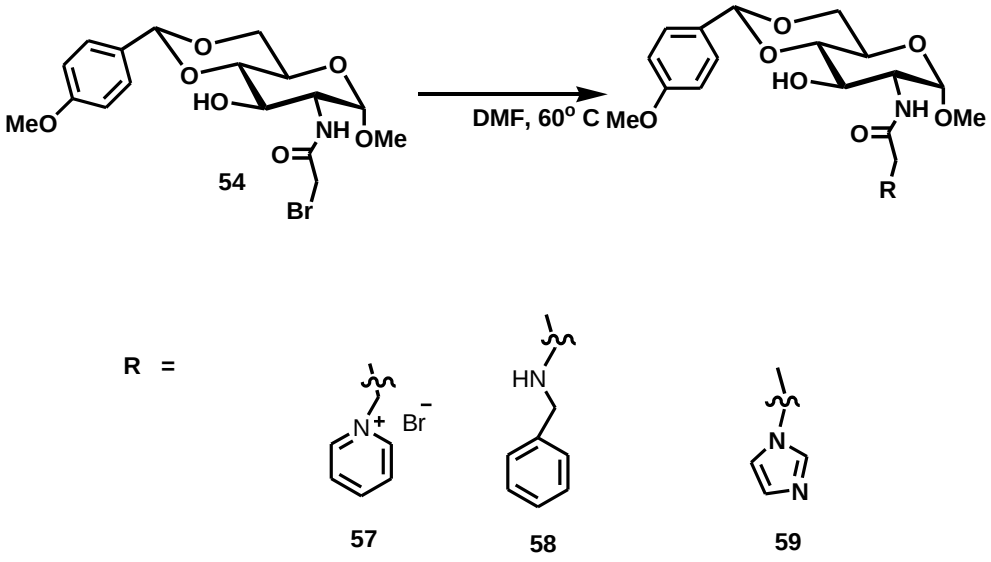



**Scheme 6.** Synthesis of 4,6-O-*p*-methoxy benzylidine acetal head group.

Compound **49** was used to furnish a variety of amide derivatives, **48-56**, as shown in Scheme 6 (compound **48** is the synthetic precursor to **49**). Compound **49** was dissolved in anhydrous dichloromethane, along with a catalytic amount of pyridine or potassium carbonate, and the reaction mixture was cooled to $0^{o}$ C. The corresponding acid chloride was added drop wise to the reaction, which was warmed to room temperature and allowed to stir for 8-10 hrs. Purification of the crude product by flash chromatography gave desired the amide derivatives **50-56**. Gel testing of the compounds was conducted and the results are shown in Table 5.




**Scheme 7.** Synthesis of amide derivatives of p-methoxy benzylidene acetal head group.




**Scheme 8.** Synthesis of p-methoxybenzylidene protected heterocyclic derivatives of glucosamine.

Compound **54** reacted with 2 equivalents of pyridine, benzyl amine or imidazole in DMF at 60°C. to give compound **57, 58,** and **59** respectively, and tested for their gelation activity in hexane, ethanol, water, ethanol: water 1:2 and DMSO:water 1:2. The results of the gel testing are shown in Table 5.

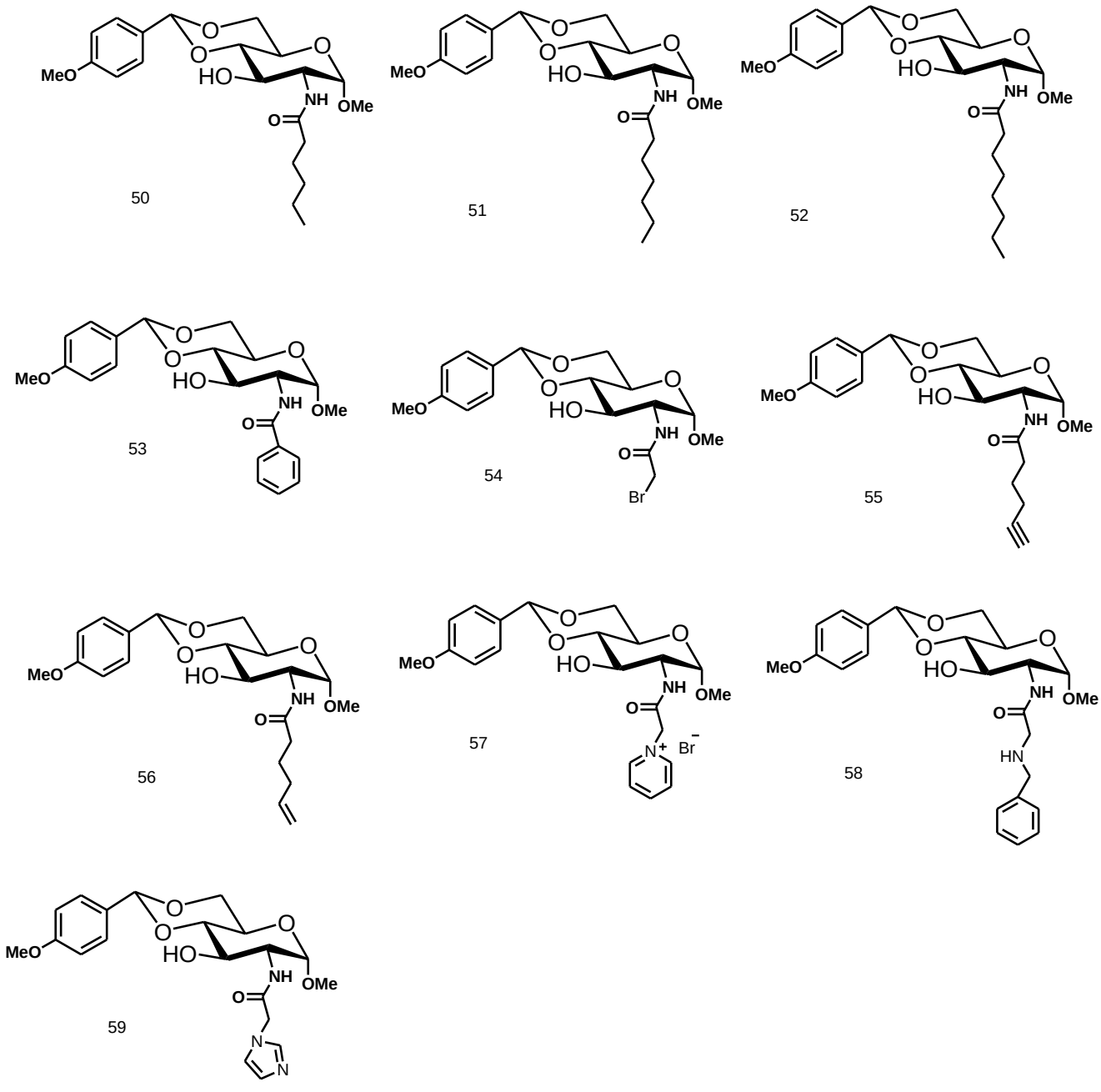



**Figure 10**. Structures of synthesized amide derivatives.

**Table 5:** Gelation test results for amide derivatives of **49**. Positive gelation results are listed in mg/mL. Legend: *-Unstable gel, I – insoluble, P – precipitate, S – soluble at 20 mg/mL

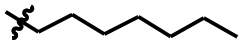
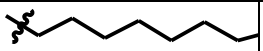
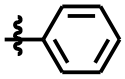
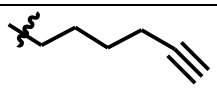
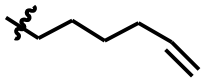
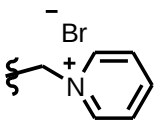
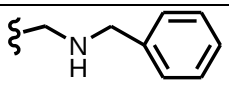
| | Structures of R | Hexane | Ethanol | Water | DMSO:$H_2O$ (1:2) | EtoH:$H_2O$ (1:2) |
|---|---|---|---|---|---|---|
| **48** |  | I | S | 10 | 7.4 | 8.0 |
| **50** |  | I | 20 | I | 5.4 | 6.0 |
| **51** |  | I | 20 | I | 5.7 | 5.7 |
| **52** |  | I | 10 | I | 4.6 | 8 |
| **53** |  | I | 8.0 | I | 5.7 | 10 |
| **54** |  | I | S | I | S | P |
| **55** |  | I | 20 * | I | 5 | 8.8 |
| **56** |  | I | S | I | 6.0 | 7.4 |
| **57** |  | I | S | S | S | S |
| **58** |  | I | 8.0 | 7.4 | 5.4 | 3.0 |

Table 5 shows that most of the compounds form gels in aqueous ethanol and aqueous DMSO, except for compounds **54** and **57**. As with the previous amide series, we have discovered that the terminal alkynyl group is not necessary for good gelation activity (compounds **50** and **55**). Compounds **48** and **58** were able to form gels in water, at concentrations as low as 10 mg/mL and 7.4 mg/mL, respectively; compound **58** also formed a gel in aqueous ethanol at concentrations as low as 3.0 mg/mL. It is believed that the nitrogen of the benzyl amine moiety in compound **58** can form an additional hydrogen bond with the methoxy group of the p-methoxybenzylidene acetal, or that additional π-π stacking interactions between the two phenyl groups are the cause of the improved gelation.

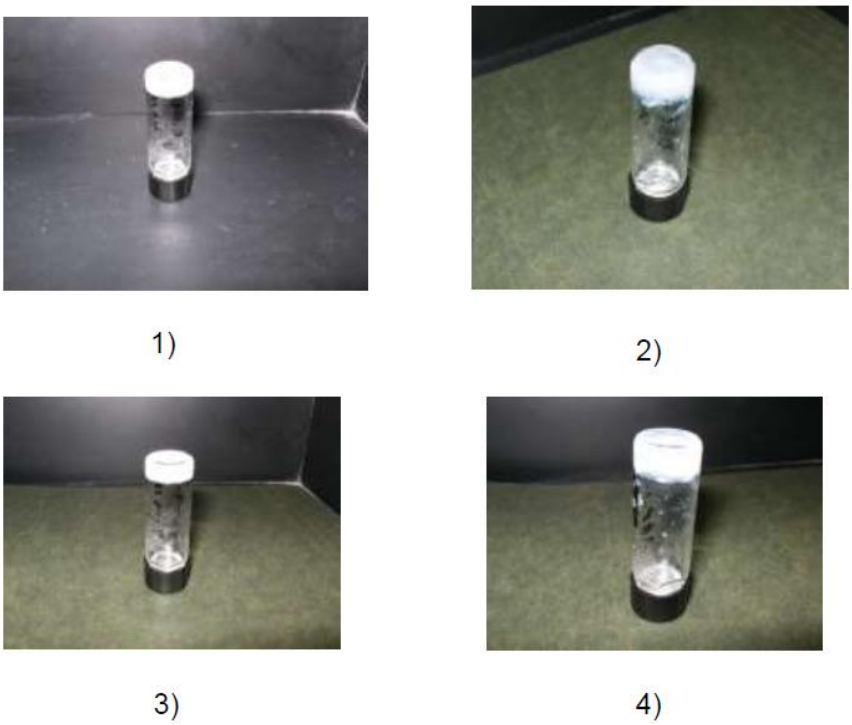



**Figure 11**. Photographs of several gels: 1) A gel formed by compound **50** at 6.0 mg/mL in EtOH:$H_2O$ (1:2). 2) A gel formed by compound **58** in $H_2O$ at 7.4 mg/mL. 3) A gel formed by compound **55** at 8.8 mg/mL in EtOH:$H_2O$ (1:2). 4) A gel formed by compound **58** in DMSO:$H_2O$ (1:2) at 5.4 mg/mL.

## Conclusions:

A series of amides were synthesized using D-glucosamine derivatives as the headgroups. The headgroups include D-glucosamine protected with 4,6-isopropylidene acetal, benzylidene acetal, and p-methoxybenzylidene acetal. The amine in the headgroups was easily functionalized with acid chloride to yield the amide derivatives. Compounds with isopropylidene acetal protective groups did not show gelation activity while compounds with benzylidene and p-methoxy benzylidene acetal are good gelators in several solvents. The amino group at the 2 position increases the gelation activity by hydrogen bonding. Free hydroxyl group at the 3 position can act as a hydrogen bond door and form a hydrogen bond. These small molecules can be useful for entrapping large biomoelcules such as enzymes and provide a good media for enzymatic reactions.

## Experimental section:

### Gelation Testing:

The compounds were tested in a vial with a rubber lined screw cap. started with 20 mg/mL concentration (2mg in 0.1mL). The mixture of Solvent and compound was heated and sonicated. The solution was allowed to cool for 15-20 minutes. If a stable gel formed, 0.1 mL of the same solvent was added and the heating/sonication and cooling was repeated. The process was repeated until the gelation concentration and the concentration prior to the unstable gel was recorded as the Minimum Gelation Concentration (MGC).[45]

### Synthesis of compound 28

The crude product was purified by flash chromatography by Hexane: EtOAc with 76% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 4.76 (d, *J* = 4.0, 1H), 3.87 (dd, *J* = 10.5, 5.2, 1H), 3.82 – 3.70 (m, 2H), 3.67 – 3.49 (m, 3H), 3.48 – 3.39 (m, 3H), 2.65 (s, 1H), 2.23 (d, *J* = 9.7, 1H), 1.50 (d, *J* = 10.9, 3H), 1.42 (d, *J* = 12.4, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 101.9, 99.7, 80.8, 72.8, 71.7, 68.9, 62.3, 55.5, 23.4.

### Synthesis of benzyl ester 30a

The crude product was purified by flash chromatography using Hexane: EtOAc with 30% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.5, 9H), 7.97 (d, *J* = 7.4, 3H), 7.68 (t, *J* = 7.5, 5H), 7.58 – 7.42 (m, 12H), 7.37 (t, *J* = 7.1, 4H), 5.95 – 5.80 (m, 2H), 5.24 – 5.07 (m, 3H), 3.91 (ddd, *J* = 21.2, 16.2, 8.6, 5H), 3.40 (s, 3H), 1.44 (d, *J* = 45.5, 7H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.9, 133.4, 135.9, 130.9, 109.8, 102.1, 82.3, 75.1, 73.2, 68.5, 62.5, 53.5, 22.6.

**Synthesis of 2-benzyl ester 30b**

The crude product was purified by flash chromatography using Hexane: EtOAc with 30% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.03 (m, 2H), 7.59 (t, *J* = 7.4, 1H), 7.52 – 7.41 (m, 2H), 5.01 (dt, *J* = 9.5, 3.8, 3H), 4.20 (t, *J* = 8.9, 1H), 3.91 (dd, *J* = 10.2, 4.7, 1H), 3.84 – 3.63 (m, 4H), 3.37 (s, 3H), 2.35 (s, 1H), 1.54 (s, 16H), 1.46 (s, 4H). $^{13}$C NMR (CDCl3, 100MHz) δ 174.9, 133.4, 129.9, 127.9, 103.8, 101.1, 76.3, 71.1, 69.0, 62.5, 55.5, 26.5.

**Synthesis of napthoyl dimer compound 31a**

The pure product was purified by flash chromatography using Hexane: EtOAc with 26% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.92 (t, *J* = 13.6, 1H), 8.73 – 8.63 (m, 1H), 8.39 – 8.24 (m, 1H), 8.08 – 7.76 (m, 6H), 7.67 – 7.30 (m, 8H), 6.05 (t, *J* = 9.6, 1H), 5.34 (dt, *J* = 13.6, 6.8, 1H), 4.95 (d, *J* = 7.4, 1H), 4.37 – 4.16 (m, 2H), 4.12 – 3.79 (m, 4H), 3.47 (s, 3H), 1.71 – 1.37 (m, 5H).

**Synthesis of napthoyl 2-ester compound 31b**

The pure product was purified by flash chromatography using Hexane: EtOAc with a yield of 36%. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, *J* = 8.3, 1H), 8.68 (d, *J* = 9.1, 1H), 8.29 (d, *J* = 7.3, 1H), 7.91 (tdd, *J* = 18.3, 15.0, 7.9, 5H), 7.58 – 7.33 (m, 7H), 6.05 (t, *J* = 9.5, 1H), 5.35 (dd, *J* = 10.0, 3.7, 1H), 5.23 (d, *J* = 3.7, 1H), 4.34 – 4.14 (m, 2H), 4.09 – 3.79 (m, 4H), 3.43 (d, *J* = 25.9, 3H), 1.72 – 1.36 (m, 5H).

**Synthesis of heptanoyl dimer compound 32a**

The pure product was purified by flash chromatography using Hexane:EtOAc with a yield of 22%. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 4.92 (d, *J* = 3.7, 1H), 4.75 (dd, *J* = 9.7, 3.8, 1H), 4.02 (td, *J* = 9.3, 2.8, 1H), 3.88 (dd, *J* = 10.5, 5.0, 1H), 3.77 (t, *J* = 10.3, 1H), 3.72 – 3.55 (m, 2H), 3.36 (s, 3H), 2.40 (t, *J* = 7.5, 2H), 2.27 (d, *J* = 2.8, 1H), 1.73 – 1.60 (m, 1H), 1.58 – 1.22 (m, 21H). ) $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.8, 101.1, 99.4, 81.9, 72.3, 68.3, 64.5, 63.5, 53.9, 36.6, 30.9, 28.9, 25.6, 21.7, 14.6.

**Synthesis of heptanoyl 2-ester compound 32b**

The pure product was purified by flash chromatography using Hexane:EtOAc, product yield was 15%. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 5.42 (t, *J* = 9.5, 1H), 4.96 – 4.81 (m, 1H), 4.75 (dd, *J* = 9.7, 3.8, 1H), 4.02 (td, *J* = 9.3, 2.8, 1H), 3.88 (dd, *J* = 10.4, 5.0, 1H), 3.83 – 3.70 (m, 1H), 3.70 – 3.54 (m, 2H), 3.37 (d, *J* = 3.2, 3H), 2.44 – 2.36 (m, 2H), 1.72 – 1.58 (m, 2H), 1.58 – 0.81 (m, 24H) $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.9, 102.1, 99.0, 82.3, 71.0, 69.0, 65.5, 62.5, 54.2, 36.9, 31.7, 29.0, 25.8, 22.7, 14.2

**Synthesis of benzylidene benzyl amine compound 35**

The compound was purified by flash chromatography using Hexane:DCM: MeOH, the pure product was obtained in 91% yield. $^{1}$H NMR (400 MHz, DMSO) δ 7.73 (t, *J* = 11.0, 1H), 7.43 (d, *J* = 4.8, 3H), 7.39 – 7.33 (m, 5H), 7.33 – 7.15 (m, 11H), 5.59 (d, *J* = 10.6, 1H), 5.25 (t, *J* = 8.0, 1H), 4.64 (t, *J* = 6.3, 1H), 4.16 (dt, *J* = 11.4, 5.8, 1H), 3.87 (td, *J* = 9.8, 3.6, 1H), 3.78 – 3.47 (m, 12H), 3.09 (dd, *J* = 26.9, 16.2, 8H), 2.44 (dd, *J* = 34.0, 4.5, 14H). $^{13}$C NMR (100 MHz, DMSO) δ

171.9, 140.7, 138.4, 129.6, 128.9, 128.8, 101.6, 99.4, 82.4, 68.7, 68.7, 63.3, 55.3, 53.9, 52.5, 52.0, 40.6, 40.4

**Synthesis of pyridinium acetamide compound 36**

The compound was purified by flash chromatography using Hexane:DCM: MeOH, the pure product was obtained in 89% yield. $^{1}$H NMR ($CDCl_3$, 400MHz) δ (ppm) 8.83(dd, *J* = 1.5, 5.5 Hz, 2H), 8.49 (td, *J* = 1.5, 8.1 Hz, 1H), 8.02 (dd, *J* = 6.6, 7.7 Hz, 2H),7.45-7.41 (m, 2H), 7.30-7.25 (m, 3H), 5.56 (s, 1H), 4.71 (m, 1H), 4.23-4.18 (m, 1H), 4.09 (dd, *J* = 3.7, 10.3 Hz, 1H), 3.92 (pt, *J* = 9.5, 9.9 Hz, 1H), 3.82-3.72 (m, 3H), 3.62 (t, *J* =9.2 Hz, 1H), 3.43 (s, 3H). $^{13}$C NMR (CDCl3, 100MHz) δ 166.4, 147.8, 146.8, 138.0, 129.8, 128.7, 128.7, 128.4, 128.1, 126.8, 103.3, 100.4, 81.9, 70.6, 69.2, 64.3, 56.3

**Synthesis of imidazole derivative with isopropylidene head group 37**

The compound was purified by flash chromatography using Hexane:DCM:MeOH, the pure product was obtained in 89% yield. $^{1}$H NMR (400 MHz, DMSO) δ 8.30 (t, *J* = 14.5, 1H), 7.60 (s, 1H), 7.40 (dd, *J* = 29.7, 4.3, 6H), 6.82 (d, *J* = 41.6, 1H), 4.69 (s, 2H), 4.63 (d, *J* = 3.4, 1H), 4.16 (dd, *J* = 9.9, 4.6, 1H), 3.83 (dt, *J* = 27.3, 9.7, 2H), 3.77 (s, 6H), 3.32 (d, *J* = 18.0, 21H), 3.06 (dd, *J* = 14.5, 7.2, 2H), 2.48 (s, 7H). ). $^{13}$C NMR (100MHz, DMSO) δ 170.1, 140.3, 130.5, 128.7, 128.5, 127.4, 103.0, 100.1, 82.7, 70.1, 69.7, 63.8, 37.9

**Synthesis of Head group compound 40**

The crude product was purified by flash chromatography using Hexane:DCM:MeOH. The pure potion of the compound isolated was 84%. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 5.27 (d, *J* = 24.2, 1H),

4.64 (d, *J* = 3.6, 1H), 3.86 (dd, *J* = 10.5, 5.2, 1H), 3.75 (t, *J* = 10.4, 1H), 3.67 – 3.47 (m, 4H), 3.42 – 3.34 (m, 4H), 2.74 (dd, *J* = 9.3, 3.7, 1H), 1.60 – 1.39 (m, 10H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.2, 102.1, 101.5, 82.2, 72.1, 69.3, 62.8, 56.9, 55.7, 26.4, 23.3

**Synthesis of Head group compound 41**

Crude product was purified by flash chromatography using Hexane:DCM;MeOH. The pure product was obtained with the yield of 71%. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 4.64 (d, *J* = 3.7, 1H), 3.85 (dt, *J* = 8.0, 4.0, 1H), 3.78 (s, 2H), 3.75 (s, 1H), 3.73 (s, 1H), 3.67 – 3.45 (m, 4H), 3.40 – 3.33 (m, 4H), 2.73 (dt, *J* = 9.2, 4.6, 1H), 1.43 (dd, *J* = 34.8, 19.2, 10H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 100.1, 98.8, 74.8, 70.9, 63.1, 62.4, 56.9, 54.9, 29.2

**Synthesis of isopropylidine head group compound 42**

The crude product was purified by flash chromatography using Hexane: DCM: MeOH, pure portion of isolated product was 87%. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.6, 2H), 6.88 (d, *J* = 8.7, 2H), 5.49 (s, 1H), 4.67 (d, *J* = 3.6, 1H), 4.25 (dd, *J* = 9.5, 4.2, 1H), 3.83 – 3.66 (m, 7H), 3.49 – 3.36 (m, 4H), 2.77 (dd, *J* = 9.6, 3.6, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.8, 102.1, 101.5, 82.2, 72.1, 69.3, 62.8, 56.9, 55.6, 55.5, 20.5

**Synthesis of isopropropylidine imidazole derivative 43**

The compound was purified by flash chromatography using Hexane:DCM:MeOH, pure portion of isolated product yield was 91%. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 9.1, 1H), 7.66 – 7.30 (m, 7H), 5.27 (d, *J* = 12.6, 1H), 4.67 (d, *J* = 3.8, 1H), 4.12 (td, *J* = 9.5, 3.8, 1H), 3.89 – 3.85 (m, 1H), 3.76 (td, *J* = 12.9, 5.1, 5H), 3.67 – 3.57 (m, 2H), 3.46 – 3.30 (m, 5H), 3.29 (s, 1H), 3.24

(s, 1H), 1.47 (d, $J$ = 10.8, 4H), 1.45 (s, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.1, 139.6, 128.8, 124.6, 100.0, 99.2, 80.9, 74.4, 63.5, 62.5, 55.4, 45.5, 55.2, 19.3

**Synthesis of benzyl amine derivative of isopropylidene head group compound 44**

The crude product was purified by flash chromatography using Hexane: DCM: MeOH, the pure product was obtained as a white powder in 86% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, $J$ = 9.1, 1H), 7.37 – 7.20 (m, 7H), 5.26 (d, $J$ = 12.6, 1H), 4.63 (d, $J$ = 3.8, 1H), 4.12 (td, $J$ = 9.5, 3.8, 1H), 3.88 – 3.82 (m, 1H), 3.74 (td, $J$ = 12.9, 5.1, 5H), 3.65 – 3.57 (m, 2H), 3.46 – 3.30 (m, 5H), 3.27 (s, 1H), 3.23 (s, 1H), 1.49 (d, $J$ = 10.8, 4H), 1.45 (s, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.1, 155.4, 139.5, 128.8, 128.4, 127.6, 100.1, 99.2, 74.9, 71.1, 63.5, 62.5, 55.4, 53.5, 51.9, 29.3, 19.3

**Synthesis of pyridine derivative of isopropylidene head group compound 45**

The crude of the product was dried and product was obtained as a white powder with the yield of 91%. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, $J$ = 6.3, 2H), 8.42 (t, $J$ = 7.3, 1H), 7.96 (t, $J$ = 6.8, 3H), 5.67 (d, $J$ = 15.8, 1H), 5.52 (d, $J$ = 15.8, 1H), 4.61 (d, $J$ = 3.5, 1H), 3.97 (dd, $J$ = 10.0, 3.6, 1H), 3.73 (ddd, $J$ = 26.5, 13.4, 7.1, 5H), 3.63 – 3.38 (m, 17H), 3.37 – 3.21 (m, 8H), 1.43 (s, 5H), 1.31 (d, $J$ = 28.4, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.6, 146.4, 145.9, 127.8, 100.1, 98.9, 74.3, 69.5, 63.6, 62.4, 62.3, 55.9, 55.5, 55.2, 29.0, 19.0

**Synthesis of compound 47**

About 10 gm of p-anisaldehyde was dissolved in 30mL of methanol in 250 mL of round bottom flask (RBF). 1.2 equivalents of triethyl orthoformate were added into the reaction flask. Catalytic

amount of PTSA was added into RBF. Reflux the reaction at 75$^{o}$ C for 8 hrs. Neutralize the reaction with 2 equivalents of sodium methoxide and filtered it. Resulting liquid was concentrated and dried it. Product was yellowish color liquid with 89% yield.

**Synthesis of head group 49**

5.00g of *N*-Acetyl-D-glucosamine was dissolved in 50 mL of methanol. The reaction mixture was refluxed with Amberlite IR-120 resin (5.00 g) over night. Resin was filtered by methanol, which was removed by drying in high vacuum pump to yield 4.9 g (90%) α and β mixtures of anomers (~8:1). α/β mixtures of methyl group at the anomeric position was dissolved in 25mL of DMF, 9.5 mL of p-methoxy dimethyl benzylidene acetal, and 0.3g of p-toluenesulfonic acid at 60°C for 2hrs. DMF was removed in vacuum to yield a 5.5g (84%) white solid (mixture of α and β anomers). The α anomer was purified by column, which was then dissolved in 75 mL of refluxing 3N KOH ethanol for 18 hours. Reaction was diluted with a 2% MeOH in DCM (~150 mL) and water (2x100 mL). After drying the DCM layer over anhydrous sodium sulphate, crude was purified by column chromatography using 2% MeOH in DCM product yield was 71%.

**General procedure for the synthesis of amide**

To a 50 mL of round bottom flask 50 mg of head group was dissolved in 2 mL of THF or DCM and 2 equivalent of potassium carbonate or pyridine was added into the reaction flask. Cooled the reaction mixture at $0^{0}$ C and 1 equivalent of the corresponding acid chloride were added drop wise to the solution. The mixture was left stirring for 6-10 hrs, after which the mixture was concentrated under nitrogen. The crude residue was purified by flash chromatography using hexane/DCM/MeOH. The resulting purified compound was tested for their gelation activity.

**Synthesis of hexyl amide compound 50**

The crude product was purified by flash chromatography using Hexane: DCM: MeOH, the pure product was obtained in 87% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.7, 2H), 6.85 (d, *J* = 8.8, 2H), 5.83 (d, *J* = 8.5, 1H), 5.49 (s, 1H), 4.69 (d, *J* = 3.8, 1H), 4.26 – 4.16 (m, 2H), 3.86 (td, *J* = 9.6, 3.2, 1H), 3.77 (d, *J* = 1.1, 4H), 3.76 – 3.71 (m, 2H), 3.57 – 3.51 (m, 1H), 3.37 (t, *J* = 5.3, 4H), 3.13 (d, *J* = 3.3, 1H), 2.22 (t, *J* = 7.7, 2H), 1.68 – 1.58 (m, 3H), 1.35 – 1.22 (m, 5H), 0.87 (dd, *J* = 7.0, 6.0, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.9, 160.4, 129.9, 127.9, 113.8, 102.1, 82.3, 71.1, 69.0, 62.5, 55.5, 55.4, 54.2, 36.8, 31.5, 25.5, 22.6

**Synthesis of heptyl amide compound 51**

The crude product was purified by flash chromatography using Hexane: DCM: MeOH, the pure product was obtained in 88% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 6.91 – 6.85 (m, 2H), 5.82 (d, *J* = 8.7, 1H), 5.53 (s, 1H), 4.71 (d, *J* = 3.9, 1H), 4.29 – 4.19 (m, 2H), 3.89 (td, *J* = 9.6, 3.2, 1H), 3.82 – 3.74 (m, 6H), 3.61 – 3.54 (m, 1H), 3.43 – 3.37 (m, 4H), 3.06 (d, *J* = 3.3, 1H), 2.29 – 2.22 (m, 2H), 1.64 (dd, *J* = 15.2, 7.6, 2H), 1.32 (dd, *J* = 15.7, 5.7, 8H), 0.88 (t, *J* = 6.9, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.9, 160.4, 129.9, 127.9, 115.6, 113.8, 102.1, 99.0, 82.3, 71.0, 69.0, 62.6, 55.5, 54.2, 36.9, 31.7, 29.0, 25.7, 22.7, 14.2

**Synthesis of octyl amide compound 52**

The crude product was purified by flash chromatography using Hexane: DCM, the pure product was obtained in 82% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.6, 2H), 6.84 (t, *J* = 12.3, 2H), 5.88 (t, *J* = 12.0, 1H), 5.47 (d, *J* = 14.9, 1H), 4.69 (t, *J* = 7.5, 1H), 4.31 – 4.14 (m, 2H), 3.85

(dd, *J* = 19.4, 9.6, 1H), 3.81 (s, 4H), 3.76 – 3.68 (m, 2H), 3.61 – 3.48 (m, 1H), 3.36 (d, *J* = 15.9, 4H), 2.31 – 2.14 (m, 2H), 1.71 – 1.54 (m, 2H), 1.38 – 1.15 (m, 9H), 0.96 – 0.79 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.5, 158.0, 127.5, 125.5, 111.4, 99.7, 96.6, 79.8, 68.4, 66.6, 60.2, 53.1, 51.8, 34.4, 29.5, 27.8, 26.9, 26.8, 21.2, 11.9

**Synthesis of benzyl amide compound 53**

The crude product was purified by flash chromatography using Hexane: DCM: MeOH, the pure product was obtained in 87% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.6, 2H), 7.52 (t, *J* = 7.4, 1H), 7.43 (dd, *J* = 12.4, 5.5, 4H), 7.26 (s, 1H), 6.88 (d, *J* = 8.8, 2H), 6.53 (d, *J* = 8.6, 1H), 5.53 (s, 1H), 4.83 (d, *J* = 3.8, 1H), 4.47 – 4.40 (m, 1H), 4.28 (dd, *J* = 9.0, 3.6, 1H), 4.01 (td, *J* = 9.7, 3.2, 1H), 3.86 – 3.74 (m, 6H), 3.62 (t, *J* = 9.0, 1H), 3.43 (s, 3H), 3.19 (d, *J* = 3.3, 1H) $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.7, 160.5, 132.2, 129.7, 128.9, 127.9, 127.4, 113.9, 102.1, 99.1, 82.2, 70.9, 69.0, 62.6, 55.6, 55.5, 54.7

**Synthesis of 5-hexynoyl amide compound 55**

The crude product was purified by flash chromatography using Hexane: DCM: MeOH, the pure product was obtained in 87% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4, 2H), 6.88 (d, *J* = 8.5, 2H), 5.90 (d, *J* = 8.7, 1H), 5.52 (s, 1H), 4.71 (d, *J* = 3.7, 1H), 4.30 – 4.19 (m, 2H), 3.89 (td, *J* = 9.5, 2.8, 1H), 3.83 – 3.71 (m, 6H), 3.56 (t, *J* = 9.0, 1H), 3.38 (d, *J* = 23.2, 4H), 2.99 (d, *J* = 3.1, 1H), 2.40 (t, *J* = 7.3, 2H), 2.28 (dd, *J* = 8.0, 5.1, 2H), 1.99 (s, 1H), 1.88 (dt, *J* = 13.2, 6.7, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.8, 160.5, 129.8, 127.9, 113.9, 102.1, 99.0, 82.2, 75.8, 71.1, 69.6, 69.0, 62.6, 55.5, 55.5, 54.2, 35.2, 24.1, 17.8

**Synthesis of pyridine amide 57**

The crude product was purified by flash chromatography using Hexane: DCM: MeOH , the pure product was obtained in 90% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 5.8, 2H), 8.33 (dd, *J* = 15.2, 8.0, 2H), 7.88 (t, *J* = 7.0, 2H), 7.27 (d, *J* = 4.8, 1H), 6.72 (d, *J* = 8.6, 2H), 5.53 (d, *J* = 15.9, 1H), 5.41 (d, *J* = 15.9, 1H), 5.37 (s, 1H), 4.58 (d, *J* = 3.4, 1H), 4.10 (dd, *J* = 9.9, 4.5, 1H), 4.00 – 3.82 (m, 13H), 3.75 – 3.56 (m, 7H), 3.42 (t, *J* = 9.2, 1H), 3.29 (s, 4H), 3.20 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.6, 160.3, 146.3, 145.9, 129.8, 127.8, 127.7, 115.6, 113.6, 101.9, 98.6, 98.4, 81.7, 68.9, 62.7, 62.4, 55.4, 55.3, 55.0

**Synthesis of benzyl amide derivative 58**

The crude product was purified by flash chromatography using Hexane: DCM: MeOH, the pure product was obtained in 87% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.1, 1H), 7.42 (d, *J* = 8.7, 2H), 7.37 – 7.24 (m, 6H), 6.87 (d, *J* = 8.6, 2H), 5.51 (s, 1H), 4.68 (d, *J* = 3.8, 1H), 4.26 (dd, *J* = 9.2, 3.8, 1H), 4.18 (td, *J* = 9.6, 3.8, 1H), 3.90 (t, *J* = 9.6, 1H), 3.84 – 3.75 (m, 5H), 3.75 – 3.68 (m, 3H), 3.56 (t, *J* = 9.0, 1H), 3.43 – 3.35 (m, 4H), 3.29 (s, 1H), 3.24 (d, *J* = 3.7, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.2, 160.4, 139.5, 129.9, 128.8, 128.4, 127.9, 127.7, 113.9, 102.1, 99.2, 82.2, 70.8, 69.1, 62.6, 55.9, 55.5, 54.0, 53.9, 51.9

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