Synthesis and characterization of sugar based low molecular weight gelators

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Synthesis and Characterization of Sugar Based Low Molecular Weight Gelators

A Dissertation

Submitted to the Graduate Faculty of the University of New Orleans in partial fulfillment of the requirements for the degree of Doctor of Philosophy in The Department of Chemistry

By

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May 2012
Dedicated to:

All my family members, friends
Acknowledgements:

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**Abstract**

Low molecular weight gelators (LMWGs) have gained great attention over the past two decades. These compounds form self-assembled fibrous networks like micelles, cylindrical, sheets, fibers, layers and so on. The fibrous network entraps the solvent and form gel. LMWGs are interesting compounds with many potential applications in material and biomedical sciences.

Many different structures have been found to be good LMWGs. Our interests focus on the carbohydrate based LMWGs. Previously, we have found that several ester derivatives of 4, 6-O-benzylidene-α-methyl-D-glucopyranoside are good gelators for organic solvents and aqueous solutions. In this study, in order to understand the structure requirement, we systematically investigated the influence of sugar head groups and the attached hydrophobic tails towards gelation. First we investigated different anomeric position functional groups in compound 1, 2. And then functional group at 4, 6 positions are studied in compound 3.

![Compounds 1, 2, and 3](image1.png)

The D-glucosamine derivatives are also studied with different functional groups at 4, 6 positions in compounds 4, 5, 6, and 7.

![Compounds 4, 5, 6, and 7](image2.png)
The design, synthesis and gelation properties of esters, amides, ureas, carbamates derived from sugar head groups shown above will be discussed in chapter II, III, IV.

Keywords: low molecular weight gelator, monosaccharide, glucosamine.
Chapter I

Introduction

Abstract: Low Molecular Weight Gelators (LMWG) usually refer to small molecules with molecular weight lower than 3000. The gels formed by LMWGs are usually thermally reversible. The mechanism of gelation by Low Molecular Weight Gelators is still not very clear. Generally, hydrogen bonds are required to enforce the one-dimensional structure. The molecular architecture of two-dimensional and three-dimensional structures is the results of π-π interaction, hydrophobic interactions, Van der Waals forces. In the gel structure, the interactions between gel molecules and solvent molecules are very critical. The energy between these two will determine whether it will form gel. To study the interaction and gel structures, different techniques like small angle X-ray scattering (SAXS), transmission electronic microscope (TEM), scanning electronic microscope (SEM), infra-red (IR), circular dichroism (CD), nuclear magnetic resonance (NMR) and so on, have been employed. The applications of LMWG are very promising, including but not limited to DNA purification, drug delivery, enzyme immobilization, tissue engineering, controlled release of biological agents, liquid crystalline materials, biosensing, and environment remediation. In this chapter, all above mentioned aspects of LMWG will be briefly reviewed.

Keywords: self-assembly, Low Molecular Weight Gelator, gelation.
1.1 General Introduction of Gel

Gel is widely used in cosmetic products, lubricants, medicines and food processing. A gel is mostly liquid which is trapped in a three dimensionally cross-linked structure. Different materials are found to be gelators. By molecular weight, gelators can be divided into polymers and low molecular weight gelators (LMWGs). Most of gels that we see in our daily life are formed by polymers. The internal cross-linked structures of polymer gels are formed by covalent bonds. Some examples are shown in Figure 1.1.

![Figure 1.1 Examples of polymer gelators](image)

Because of strong chemical bonds, polymer gels are stable and typically thermally irreversible. They also have a distribution of molecular weight. However, for LMWGs, the cross-linked structures of a gel are formed by non-covalent bonds. These include hydrogen bonds, Van der Waals forces, hydrophobic interactions, \( \pi-\pi \) interactions and so on. Some examples are shown in Figure 1.2.
In comparison with polymer gel, the mechanism of gel formation by LMWGs is also different. What is now accepted by most researchers is the three steps gelation process.  

First, gelator molecules are aggregated in one dimension by multiple non-covalent interactions like hydrogen bond. Second, micelles, vesicles, fibers, ribbons or sheets are formed. Third, interactions between fibers or sheets lead to network which trap solvent molecules and form the final gel. Because physical bonds are not as stable as chemical bonds, the gels are thermally reversible.

By different gel solvents, gelators can be divided into hydrogelators and organogelators. The driving forces of gels formed by hydrogelators are hydrophobic force. There are examples from both polymers and low molecular weight gelators.
Because the resulting gels’ aqueous environment, hydrogelators are very useful in application for human health. Hydrogels are currently used as scaffolds to contain human cells to repair tissue. Electroencephalography and electrocardiography use hydrogel as electrodes. Contact lenses are made of silicone hydrogels, polyacrylamide. Organogelators depend on hydrogen bonds, Van der Waals forces and other non-covalent forces to form gel in organic solvents.

If the liquid is removed from the gel’s cross-linked networks, the resulting structure will have extremely low density and thermal conductivity. Different drying processes produce aerogel and xerogel. An aerogel is made by supercritical drying, and a xerogel is made by unhindered shrinkage.
1.2 Gel Preparation

The gel formation process can be triggered by different factors. Temperature change is one of the most common ways to make a gel. Typically, a 2-3 mg sample is weighed and transferred into a small vial, the test solvent was added. The sample is usually dissolved by heating and left at room temperature for gelation to happen.\textsuperscript{32,33} The limitation of using heat in biological application is obvious, so different methods are developed.\textsuperscript{34} These are discussed in the following.

Changing solution pH is usually carried out by adding a diluted acid/base, or adding another reagent which can cause hydrolysis of the compound in the solution.\textsuperscript{35,36} For example, through the neutralization of aqueous alkaline solution of scleroglucan, the scleroglucan gel formed in situ with a structure of cross-linking of the polysaccharide\textsuperscript{37} In this case, formamide or ethyl acetate was added.

Adding another reagent usually triggers a reaction which yields the compound that can form gel in test solvents.\textsuperscript{38} This usually refers to as in situ gelation. The following reaction was carried out in a DMSO and water mixture.\textsuperscript{39} Two equiv ceric ammonium nitrate (CAN) was used and after the reaction is completed, a gel formed in a 2 to 1 ratio DMSO and water mixture.
Triggered mechanisms are not limited to oxidation or reduction reactions. Ligand-receptor interaction, enzyme reactions in biological system can also be used to introduce gelation. In a recent paper,\textsuperscript{40} thermolysin was used in a solution of the short tetrapeptide FEFK. In the solution, hydrolysis of thermolysin happened and after certain amount of time the equilibrium was reached. At the same time, the short peptides self-assembled into antiparallel $\beta$-sheet which further assembled into fibers and then led to gelation. Bing Xu’s group use a kinase/phosphatase switch to control a supermolecular hydrogel.\textsuperscript{41} In the presence of adenosine triphosphates (ATP), hydrogelator Nap-FFGEY is treated with kinase, which leads to a gel-sol phase transition.

Light can also be used to trigger gelation.\textsuperscript{42,43} One example is the photocaged peptide VKVKVKVKV\textsuperscript{D}PPTKVKKV-KV-NH$_2$.\textsuperscript{44} The X structure is shown in Figure 1.5. The 2 wt % solution of this peptide in water was very stable under the ambient light. But when the solution was treated with ($260 < \lambda < 360$ nm) light, the peptide begin to fold and produce amphiphilic $\alpha$-hairpins which further assemble into fibers and lead to the gelation.
Magnetic field is another factor that can change the gel performance. The engineers at Harvard and Duke Universities were able to make a magnetic field controlled gel sponge. The macroporous ferrogel was mixed with magnetic iron nanoparticles. When a magnetic field is applied, the gel can be compressed to as much as 70%. Laura J. Kaufman from Columbia University used surface-modified magnetic beads in collagen solution to align thin collagen gels. Their research showed when the magnetic beads were coated with streptavidin lead (metal), the alignment is the best.

Ultrasound has also been used for the formation of gels. A recent example used this method. The compound 10 forms a gel in N, N-dimethylformamide (DMF) with the sonication treatment. The gelation concentration is 0.85% in DMF. The sonication source is an ultrasonic cleaner (0.45W/cm², 40kHz, 30s).
Besides these mentioned methods, there are also other methods like electric field\textsuperscript{48} adding metal ion\textsuperscript{49, 50} and multiple stimuli\textsuperscript{51}. 

Figure 1.6 An example of ultrasound triggered gelator
1.3 Low Molecular Weight Gelators (LMWGs).

LMWGs have gained people’s attention for the last two decades. Even though the design of LMWGs is sometimes depending on luck, researchers are able to find gelators from different classes of compounds including but not limited to acids, ureas, amides, carbamates, esters, carbohydrate, steroids, nucleotides, nucleosides, amino acids, alcohol etc. Some examples are shown in Figure 1.7.\textsuperscript{52-73}

Figure 1.7 Examples of LMWGs from different classes. Amide gelator, urea gelator, steroid based gelator, ester gelator, alcohol gelator, nucleotide gelator, nucleoside gelator.
With the help of modern instruments like small angle X-ray scattering (SAXS), circular dichroism (CD), solid phase nuclear magnetic resonance (NMR), differential scanning calorimetry (DSC), the understanding of gelation mechanisms and gelation structure relationship of LMWGs are significantly improved. The design of LMWGs usually requires balance of polarity, hydrophobic interaction and functional groups that can interact with solvent molecules.\textsuperscript{74,75}

1.3.1 Carbohydrate based Low molecular weight gelator

Being different from some expensive materials, carbohydrate is natural and inexpensive. The abundance and availability of carbohydrate are not the only reasons, structures of carbohydrate also give people different functional groups to play with. Carbohydrate has several hydroxyl groups which are available for introducing other functional groups like urea, amide, carbamate. The hydroxyl groups are very good hydrogen bonding donor, which will be very useful in gel formation.

Figure 1.8 The structures of typical sugars
The study of carbohydrate as gelator started about several decades ago. Different approaches were taken to modify carbohydrate structures. Carbohydrate polymer was explored first.

Carbohydrate polymer is one of many naturally occurring polymers. Starches consist of amylose which is made by chain polymers of α-D-glucose and amylopectin is a branched structure of glucose polymer. Cellulose is a glucose polymer linked by beta-linkage. Bacterial cell wall is mainly composed of polysaccharides. To make carbohydrate polymer to function as a gelator usually requires structure modification of the polymer or attach another component to the polymer.

Mazzei Franco’s research group synthesized a hydrogel using polysaccharide scleroglucan and borax (sodium borate) as cross-linking agent. The hydrogel was used in immobilization of redox protein on electrodes materials to study electron transfer mechanisms related with redox biomolecules. Unlike chemical cross-linking agents hydrogel can provide gentle environment for biomolecules. The porous structure also facilitates exchange of aqueous solution.
Scleroglucan has a triple helix conformation and it is very stable even at 90°C and up to pH=12. In their preparation, 20 μL of Scleroglucan (Sclg) hydrogel solution (1% w/v) was mixed with 14 μL of 0.015M borax solution (Sclg/borax equivalent ratio=1:1) and then test protein was added to achieve a final concentration of 2.5x10^{-5} M. The pyrolytic graphite electrode was covered by the solution and dried at room temperature. Three heme proteins (hemoglobin, myoglobin, horseradish peroxidase) were tested. The study of direct electrochemistry showed the peaks corresponding to the electron transfer between protein and electrode. The study also revealed that only the inner layer of hydrogel on the surface of electrode are responsible for electron transfer, which contribute to the showed redox peaks. Hydrogen peroxide was used to test biocatalytical property, results confirmed that protein in the hydrogel maintain biological activity.

The development of carbohydrate based LMWGs are later than carbohydrate based polymers. At the early period, glucose, mannose, galactose, glucosamine and small function
groups were studied. In 1998, Seiji Shinkai group from Kyushu University protected monosaccharides (D-glucose, D-galactose and D-mannose) at 4, 6 positions using benzaldehyde and ZnCl₂. The reaction is more like a protection of hydroxyl groups. The products are shown in Figure 1.10.

![Figure 1.10 The products of 4, 6 position protected sugars](image)

Compound 21 was a good gelator (gelation concentration is 1.0 wt %) in different organic solvents like cyclohexane, benzene, toluene, p-xylene, CCl₄, CS₂. Compound 22 formed gel in the long chain alkanes like n-hexane, n-heptane, n-octane. Later, Seiji Shinkai’s group screened more α-sugar structures and explored β-sugars. The β-sugars are shown in Figure 1.11.

![Figure 1.11 Structures of β sugar derivatives](image)
Thirty four solvents were tested in gelation properties. Compound 25 derived from β-mannose behaved best and it formed gel in twelve solvents. Compound 23 derived from α-mannose was the second and it gelled 10 solvents.

To understand the interaction between gelator molecules, Seiji Shinka’s group obtained gelators’ X-ray crystal structures. The arrows represent hydrogen bonds.

Figure 1.12 Illustration of hydrogen bonds in the crystal structure of compound 21
As we mentioned above the first step of gelation is usually the formation of hydrogen bond or other intermolecular interaction between gelator molecules. The X-ray crystal structure proved that there were two hydrogen bonding sites in the structure locating at 2-OH and 3-OH. Judging from the gel tests results, compound 21 is a good gelator in six solvents like benzene, toluene, p-xylene and so on.

Compound 28 also have two hydrogen bond donors, but there is only one used for intermolecular connection. The other one is used for intramolecular interaction between 3-OH and 1-OMe. The crystal structure is shown in Figure 1.13. In comparison with compound 21, 28 is not a good gelator at all. It didn’t form gel in any test solvent.

Figure 1.13 The illustration of hydrogen bonds in compound 28
The Figure 1.14, 1.15 show the crystal structures of compound 29 and 30. As we can see, for compound 29, there is only a two dimensional layer and no one-dimensional array. Compound 30 did not have any intermolecular interaction. Compound 29 and 30 are not gelators.

Figure 1.14 The illustration of hydrogen bonds in compound 29, arrows indicate hydrogen bonds.
The X-ray diffraction (XRD) provides researchers insights of crystal structure and gelation. It is now widely used in identification of gel structure.

Seiji Shinkai’s group did not stop at using small protecting groups at hydroxyl positions. They expanded their research by linking to other classes of compounds. The conjugated structure of porphyrin provides π-π stacking interaction, but porphyrin is not a gelator in any solvent, therefore they introduced carbohydrate in porphyrin.\(^2\)
5,10,15,20-Tetrakis- (4-carboxyl-1-phenyl)porphyrin reacted with \( p \)-aminophenyl-2,3,4,6-tetra-\( O \)-acetyl-\( \alpha \)-D-galactopyranoside to give the target molecule. The molecule cannot dissolve in most solvents (benzene, toluene, THF, MeCN, anisole water, \( i \)-PrOH, \( n \)-BuOH, chloroform, dichloromethane, \( n \)-hexane), but is soluble in DMF. Gelation tests were carried out in mixed DMF solvent. The molecule can gel DMF/MeOH, DMF/EtOH, DMF/\( i \)-PrOH at 1:4 ratio, at 3.0 wt\%. In 1:19 ratio DMF/benzyl alcohol mixture, the critical gelation concentration is 0.1 wt\%. In alcoholic solvent, the molecule tended to form flat structure, which gives more \( \pi \)-\( \pi \) interaction and hydrogen bonds. In aprotic solvents, there were more intramolecular interactions and those interactions lead to distortion of flat structures.

Santanu Bhattacharaya’s group also developed a series of tetrameric sugar derivatives. An azobenzene core was attached with four carbohydrate modified structures.\textsuperscript{83}

\begin{center}
\includegraphics[width=0.5\textwidth]{image1.png}
\end{center}

\textbf{Figure 1.17} The derivatives of azobenzene compounds
The gel tests showed that compound 31a is the only one that can form gel in water. The resulting solution formed gel immediately at a concentration of 0.1 wt%. Gelation was also tested under various pH conditions, compound 31a can form gel from pH 4 to 10. Different solutions (1mM) of NaCl, MgCl₂, KCl, CaCl₂ were also tested. Compared with spongy globule formed in water, in 1 mM CaCl₂ it formed rodlike fibers, in 1 mM MgCl₂ it formed fibrillar globules, and in 1 mM NaCl it formed aggregated spheres. The information of fibers was confirmed from scanning electron microscope (SEM). SEM is very useful in the gel morphology study, although fibers are from xerogel without solvent, it can still provide researchers with insights about fiber appearance and how fiber aggregate.

To further study structure and gelation relationship, azobenzene core was changed to bis-amide derivative of terephthalic acid. Another three compounds were synthesized. However none of them can form gel.

![Figure 1.18 The derivatives of bis-amide azobenzene](image)
In this study π-π stacking from azobenzene and hydrogen bond are the driving force for gelation. Circular dichroism (CD) study showed that stacking of azobenzene arranged in a right-handed helical structure.

The hydrophobic interaction is one of the most important factors that lead to gelation. The carbohydrate itself is usually very polar. To change it, some researchers like Seiji Shinkai protected hydroxyl groups. Some others like Santanu Bhattacharaya linked big nonpolar molecule to the carbohydrate to balance the polarity. Toshimi Shimizu’s group linked β-hydroxyl group of glucose with long chain unsaturated alkane to form aryl glycolipids.\textsuperscript{84}

![Chemical structures](image)

**Figure 1.19** The structures of aryl glycolipids

The compound 33 could form gels in water/alcohol mixture and several organic solvents. The gelation ability decreased with the increasing of unsaturation. Compound 35 cannot form gel in any test solvent. The gel sample was made in thin capillaries and X-ray diffraction (XRD) was
measured. The results suggested that compounds 33, 34 formed ordered bilayer which packed together and trap solvent molecules between them. In the water/alcohol test solvent, the spacing for compound 33 and 34 are 3.14 nm and 3.90 nm, respectively. This data is the characteristic of \( \pi-\pi \) stacking. The packing model is shown in Figure 1.20. The column represents the long alkane chain and solid circle represents sugar group.

![Figure 1.20](image)

Figure 1.20 The illustration of molecule packing using compound 34

The same idea is found in a very recent paper. In their case, to balance the polarity they used two sugar molecules. The structure is shown in Figure 1.21.
The functional groups that linked to carbohydrate were not just helping gelation, some functional groups also bring other applications. For example, the glucose based naphthalene derivatives were synthesized by using hydrazine and diamine linkers. Four diamine linkers were studied. They were ethylenediamine, 1,3-propanediamine, 1,4-butanediamine, and 1,6-hexanediamine. Five compounds were synthesized and tested in 30 different solvents for gelation. 4 compounds can each gel more than 10 solvents. The gelation concentration is 2.5% (w/v).

Fluorescence study was used to compare the gel state and solution state. Gel is measured at room temperature, and solution is done at 80°C which is above gel melting temperature. The study showed that the intensity difference is obvious between gel state and solution state. Several factors may contribute to these results. The temperature decrease from 80°C to room temperature...
can lead to immobilization of gelator molecules. Gelation also decreased the mobility of molecules. In the end, nonradiative decay of the fluorophore moiety was suppressed and therefore fluorescence emission boosted. Structure wise, XRD studies revealed that gelator molecules are packed in a J-aggregation pattern which is featured by edge-to-edge π-π stacking from naphthalene. The hydroxyl groups of glucose formed hydrogen bonds. Together they formed layered structure and depending on the surrounding solvent, the naphthalene moiety will face inside or outside to form the tube structure and then the tubes aggregated into fibers leading to gelation.

The examples above showed the modification of one sugar molecule. To take advantage of hydroxyl groups which are very useful in hydrogen bonding, researchers introduce multiple carbohydrates into one molecule.

For example, Fraser Stoddart group linked β-cyclodextrin (β-CD) formed by 7 α-D-glucoses with a modified deoxycholic acid. The complex 38 was used as a host. The complex 39 served as guest.
Figure 1.22 The structure of complex 38

Figure 1.23 Structure of compound 39
The β-CD of host complex interacts with the *trans*-azobenzene unit of the guest complex to form supermolecular inclusion which can form a hydrogel and the gel-sol phase-transition can be triggered by light.

![Diagram of gel and solution change](image)

**Figure 1.24** The illustration of gel and solution change

The reason behind light responsive gel-sol phase-transition is the trans-cis isomerization of azobenzene. Under 355nm UV light, the trans-azobenzene lying in the cavity of β-CD was photochemically converted into *cis*-azobenzene and left the cavity. This change made hydrogel go to solution state. Under 450 nm visible light, because the process was reversed and supermolecular inclusion formed again, the solution was converted to a gel again. Circular dichroism further confirmed the gel-sol and sol-gel phase-transition.
1.3.2 Other types of Low Molecular Weight Gelators

Amino acids and peptide based LMWGs

Amino acids and peptide based gelators are another big class of LMWGs. The structure of amino acids and peptides provide hydrogen bond donor and acceptor. The nature biocompatible property of amino acids and peptides makes them the best choice in biological application. The structure of amino acids usually requires modification to have more Van der Waals forces and π-π stacking interaction. L-glycine, L-valine, L-leucine, L-lysine and so on are all used to synthesize new LMWGs. Some of these systems are summarized below.

L-lysine is the first amino acid modified to function as a gelator. In 2000, Hirofusa Shirai’s group attached different alkyl chains to L-lysine.\textsuperscript{88,89} The molecules are shown in Figure 1.25.

![Figure 1.25 Structures of L-lysine Low Molecular Weight Gelators](image-url)
Compound 40 was proved to be an excellent gelator. It formed gel in all 27 test solvents. These solvents include polar solvents like MeOH, EtOH, DMSO, unpolar solvents like hexane, cyclohexane, oil like silicone oil, salad oil. The minimum gelation concentration varied from 0.006 g/mL to 0.1 g/mL. Compounds 41 and 42 can gel 20 and 4 solvents, respectively. Compound 4 gelled 3 solvents at very high concentrations. The alkyl groups on both sides of the L-lysine provide Van der Waals between molecules. Compound 43 is a urea, which has one more hydrogen bond donor. This may contribute to the fact that compound 43 recrystallized out in 21 solvents.

A similar structure modification is found using L-alanine. The following compounds are tested in pure organic solvents; none of them can form gel. But with a little amount of water, they can gel 10 different organic solvents.

\[ \text{44: } n=5 \quad \text{44b: } n=7 \quad \text{44c: } n=11 \]
\[ \text{44d: } n=13 \quad \text{44e: } n=15 \]

Figure 1.26 The structures of L-alanine LMWGs
Peptides gelators are usually made of modified amino acids which provide more interaction among molecules. A very recent paper from Zhimou Yang group in Nankai University studied new peptide hydrogelators in cell culture and cell recovery post culture. The molecules they made by solid peptide synthesizer are shown in Figure 1.27.

![Figure 1.27 The structure of a modified peptide gelator](image)

To form a gel, phosphate buffered saline was mixed with the product. Then the reductant solution (2 equiv dithiothreitol or glutathione) was added into solution and the S-S bond was cleaved. The molecule became Ada-GFFYK<sub>n</sub> which formed hydrogel within one minute after adding reductant solution. Gelator 48a behaved the best among all the four compounds. It formed clear gel at 0.5 wt% and stayed stable for more than 3 months. The resulting hydrogel could change back to clear solution when M-β-CD was added. This feature was very useful in the cell recovery after culture analysis. Mouse embryonic fibroblast cells NIH 3T3 was used in cell culture, most cells are alive and the density kept increasing within 3 days period. The
separation of cell was done by adding M-β-CD and followed by centrifuge. Compared with cells growing on tissue culture plates, the collected cells from gels behaved normally.

Small peptides don’t have as many hydrogen bonds, so other modifications were considered. Prasanta Kumar Das and his coworkers developed a new series of small peptides with Fmoc functional group. The structures are shown in Figure 1.28.

![Figure 1.28 Structures of small peptides with Fmoc group](image)

The gelation test was carried out in water. Compounds 49-50d formed gels, which were expected by researchers. The minimum gelation concentrations ranged from 0.6 % (w/v) to 2.2 % (w/v). Compound 51 formed gel at 3.0 % (w/v). Other compounds were not gelators. The tert-
butyl group at the end of the molecule could not provide the same interaction as the Fmoc group. The wide Angle X-ray Scattering of xerogel obtained from compound \textit{50b} provided insights of packing. The Fmoc group provided $\pi$-$\pi$ interactions between molecules. The distance is 3.5 angstrom. The phenyl groups of two molecules also interacted with each other by $\pi$-$\pi$ interactions. The hydrogen bonds were from peptide bonds. The molecules packed one on another and formed a layer. Those layers also interacted with each other at a distance of 9.5 angstrom.

\textit{Planar macrocyclic molecule based LMWG}s

Planar macrocyclic molecule based LMWG\textit{s} is another class of gelators. Porphyrins, crown-based structures, and steroid are all planar macrocyclic molecules. Because of aromatic groups and planar structure, they are perfect for $\pi$-$\pi$ stacking.

\textit{Porphyrrins}

In previous section, carbohydrate was used to modify porphyrin structure. Other modifications are made by introducing long chain alkyl groups, aromatic ring, ureas, amides, carbamates.\textsuperscript{93} Seiji Sinkai’s research group systematically studied different attachments for porphyrin. In 2004, they published a paper in JACS about using long alkyl chain amide.\textsuperscript{94} The structures are shown in Figure \textbf{1.29}. 

30
Compounds 52 and 53 were excellent gelators with or without metal. Compound 54 did not gel any test solvents. Compound 55 formed gels in cyclohexane and decahydronaphthalene (Decalin). The gel in decalin showed thixotropic behavior. After the gel was shaken and broken into solution, it can reform gel without heating again. This implies that gel fibers are stable, extremely thin and extended.

More structure variations were explored by Seiji Sinkai research group. The urea structure is usually considered very efficient in forming hydrogen bonds. These compounds below show very good gelation property. The study also showed that porphyrin not just pack in one-dimensional. Compound 52 gave a one-dimension packing, but compound 59 aggregated in a two-dimension fashion.\(^\text{95}\)
Compound 58 also showed a special 2-dimensional packing. It consisted of two different hydrogen bonds.

*Crown-structure*

The crown structures like cryptand, 18-crown-6, dibenzo-18-crown-6 were also studied. In the early period, crown ethers were linked with cholesterol to make gelators. The use of cholesterol was mainly to increase the interaction among molecules. Seiji Shinkai’s research group developed a new type of crown-based gelator without cholesterol.\(^{96}\)
Figure 1.31 The structures of crown ether LMWGs

Compound 61 and 62 could form gel in benzene and \emph{m}-xylene at 5.0 wt %. With the addition of compound 63, mixtures of 61, 63 and 62, 63 both formed gels in two more solvents. With the addition of compound 64, mixtures of 61, 64 and 62, 64 both formed gel in one more solvent. Other solvents like methanol, THF, DMF were tested too. But the gelation only happened in aromatic solvents. Further study showed that the interaction between crown based molecules with guest were charge-transfer interaction.

\textit{Aromatic ring system}

Conjugate aromatic rings like perylene, coronene are another type of planar macrocyclic molecules. There are examples of tetraester coronene, imidoester coronene as liquid crystals.
Subi J. George research group used charge-transfer interaction to design coronene based hydrogel. The structures are shown in Figure 1.32. Different acceptors are screened.

![Donor Acceptor Structures](image)

Figure 1.32 The structures of aromatic based LMWGs

CS-DMV complex formed a transparent dark-red hydrogel. AFM study showed that fibers are 10-15 µm long and 100-300 nm in diameter. The gel stayed stable for several months. The X-ray study showed that CS and DMV featured in a face to face aggregation.

**Steroid**

Steroid based gelator is another class of planar macrocyclic based LMWGs. The research of steroid based gelator begun very early, which provides us a good understanding of structure and gelation relationship. Among different steroids, cholesterol and anthraquinone are well studied, because the hydroxyl group provides modification options. Long chain structures and aromatic ring systems were first explored. Structure 70 was the research result from Shin
Shinkai’s research group\textsuperscript{98} They attached the long chain functional group to the C3 position in both R and S isomers. The stereochemistry at C3 position made a big difference. The compounds with S chirality (natural chirality) showed limited gelation property. But compounds with R chirality behaved much better and they can form gels in more solvents and at much lower concentration (<1 mg/mL).

\[ \text{R} = \text{O(CH}_2\text{)}_{n}\text{H} \quad n=1-5, 10 \]

\[ \text{R} = \text{N((CH}_2\text{)}_{n}\text{H})_2 \quad n=1-3 \]

Figure 1.33 The structures of steroid based LMWGs

Richard G. Weiss research group studied the aromatic attachment of cholesterol, anthracene, naphthyl, phenyl group were linked with other functional groups like ester, carbamate to cholesterol\textsuperscript{99-101}
Compound 71 and 72 were very good gelators in different organic solvents. Compound 73, 74, 75 formed gel in some long alkyl solvents like \( n\)-dodecane, \( n\)-hexadecane and some alcohols like 1-propanol, 1-butanol, 1-pentanol. From the spectroscopy study, there was no
hydrogen bonding in the gels, so it proved the importance of aromatic groups. Weiss research group also studied different steroids with the same aromatic group at C3 position. The variation focused on different alkyl group attached to C17 position. The results showed small changes in C17 position did not have much effect in gelation and branched alkyl group gave better gelation results.

1.4 Applications of Low Molecular Weight Gelator

We have seen lots of applications from nature polymers like alginate, chitosan, fibrin, hyaluronate, collagen, gelatin and synthetic polymers like poly(acrylic acid), poly(vinyl alcohol), polyphosphazene. The applications of LMWGs are mostly on laboratory level and models study, but scientists have been working on the improvements of gelation condition, synthetic routes, toxicity, etc. There are more and more publications in different applications especially in nanomaterials and biological area.

1.4.1 LMWGs in Nanomaterials

The nano-scale gel fibers are very similar to nanotubes. The porous structure formed by fibers can be used as structure directing agents for nanoporous materials. The silica based nano structure has been well studied.\textsuperscript{102-104} To efficiently transfer gel fiber structure to silica, interaction between gel fibers and silica is required. Tetraethyl orthosilicate (TEOS) has been used in this study. Arindam Banerjee used a small amount of amino acid and graphene oxide to form a stable hydrogel. An aqueous solution of graphene oxide at 22 mg/mL was mixed with 50
μL HAuCl₄ (25 mM) and then the right amount of tryptophan was added. The solution was stirred well and sonicated to obtain a hydrogel. The addition of tryptophan was to reduce Au³⁺ to Au. This in situ Au nanoparticles formation is greener than the old method, which was done in solution by mixing graphene oxide with metal salt solution and followed by reducing agent (borohydride, hydrazine, etc) or stabilizing agent. Jianbin Huang research group reported the synthesis of photoluminescent lanthanide-organic hybrid nanofibers in hydrogels. They used europium-cholate hybrid hydrogel to transcribe europium-doped silica nanotubes. Basically, sodium cholate, europium ion, ammonium, tetraethyl orthosilicate (TEOS) were mixed well into solution. Due to hydrophobic effect and metal coordination, a hydrogel formed. The excess Eu³⁺ gathered on the surface of fibers and then negative charged silica oligomers were drawn onto fiber surface by electrostatic attraction. When the amount of silica oligomers reached certain level, silica polycondensation occurred and silica nanotube network formed. The gel was destroyed afterward and the product was collected and calcined.

For nanoporous structure, Seiji Shinkai research group did most the early work and they continue to explore new gelators for nanostructure.¹⁰⁵ The β-glucose based LWMGs can gel water/ethanol mixture and the morphology at different concentrations was studied. For compound 76, at 3.0 wt% in water, fiber thicknesses varied from 400 to 600 nm. At 0.1 wt%, thicknesses ranged from 20 to 30 nm. The solution-gel polymerization transcribed gel fiber structure onto silica. The resulting silica nanotube had two different diameters. The one from 3.0 wt% gel was 450-600 nm and the one from 0.1 wt% was 20-25 nm.
This result showed that the nanotube structure can be controlled by gelation concentration. It proved the possibility of encaging suitable materials in the nano structure.

1.4.2 Low molecular weight gelators in biological applications

The applications of LMWGs in biological area are very promising, especially for gelators based on carbohydrates, amino acids, nucleotides, and nucleosides. They can be used in controlled drug release, enzyme immobilization, etc. Different models of controlled drug release have been studied. Jan van Esch research group studied small molecules, 8-aminoquinoline (AQ) and 2-hydroxyquinoline (HQ), as model drug molecules.¹⁰⁶ The gel was formed by N, N-dibenzoyl-L-cystine (DBC) in 150 mM NaCl solution, PBS (phosphate-buffered saline at pH 7.4) and water. The AQ or HQ was mixed with gelator in test solvents. After heating and cooling process, gel formed and then same solvent was added on top of the gel to monitor the release. The top solvent was analyzed by UV-vis spectroscopy to determine the release amount. The study showed that release of AQ was slower than that of HQ. Because the interaction between AQ and gelators were stronger due to the amino group of AQ and carboxylic acid group of gelator molecule. Only for AQ, the initial release rate was related with gel degradation rate.
Peptide based LMWG\(\text{s}\) were studied for drug controlled release, too.\(^{107}\) Takatoshi Kinoshita research group studied self-assembling peptide RADA\(\text{FI}\) system and RADA\(\text{FII}\) system. Peptides mixed with model molecule to form gel and a buffer solution was added on top of the gel. The release was monitored by UV-vis every 30 minutes. The release process was controlled by Fickian diffusion. The AFM study showed the packing was different for the two systems due to aromatic groups of peptides. The packing difference also resulted in the difference of model drug release. Large model drug was easier to release from RADA\(\text{FI}\).

Enzyme immobilization is another important application for LMWG\(\text{s}\). The gel’s porous structure meets the space requirement of big protein. Besides, biocompatibility of LMWG\(\text{s}\) can maintain protein’s activity. Bing Xu research group has done extensive study in this area.\(^{108}\) They studied the combination of LMWG\(\text{s}\) (Fmoc-L-phenylalanine and Fmoc-L-lysine) with different Heme model compounds. To test the activity of peroxidase (Heme served as active center), Xu et al studied oxidation of pyrogallol. The hydrogel based artificial enzyme show the highest activity in toluene. It is 90\% of the activity of native horseradish peroxidase in water.

Other applications of LMWG\(\text{s}\) are tissue engineering, controlled release of biological agents, liquid crystalline materials, biosensing, and environment remediation and so on. More and more LMWG\(\text{s}\) are synthesized and characterized every year. More and more applications of LMWG\(\text{s}\) will be available not only in laboratory study but also in industry and daily life.
References


Chapter II

Synthesis and Gelation Properties of 1-Deoxy-D-Glucopyranoside Ester Derivatives and β-Phenyl-D-Glucopyranoside Ester Derivatives

Abstract: D-Glucose has been modified to obtain effective low molecular weight gelators. Previously, our group investigated 4, 6-O-benzylidene-methyl-α-D-glucopyranoside and modified the structure by introducing ester functional groups on 2, 3-hydroxy groups. The gelation test results showed several excellent gelators. To further investigate structure and gelation relationship, we studied the effect of anomeric position. In this chapter, two different headgroups are studied, 4, 6-O-benzylidene-deoxy-α-D-glucopyranoside 1 and 4, 6-O-benzylidene-β-phenyl-D-glucopyranoside 2. The esterification were carried out at 2, 3 positions. The long chain alkyl groups, terminal alkynes, aromatic groups were attached to the head groups. Their gelation properties were tested.

Keywords: low molecular weight gelator, D-glucose.

Part of this chapter is adapted from reference 21.
Introduction

The natural abundance and biocompatibility make carbohydrate based LMWGs the best candidate for biological applications.\textsuperscript{1-15} Seiji Shinkai’s group from Kyushu University is the first group systematically studied gelation properties of different sugars like mannose, glucose, allose, altrose.\textsuperscript{16,17} They not only studied the protected 4, 6 position but also invested α, β difference at anomeric position. However modifications at 2, 3 positions were not explored much.

The previous work done by our group studied the ester functional group at 2, 3 positions. 4, 6-O-benzylidene-methyl-α-D-glucopyranoside was treated with different acyl chlorides.\textsuperscript{18,19} The reaction usually gave three products: diester, 2-monoester, 3-monoester, as shown in Scheme 2.1.

Scheme 2.1 The synthesis of ester derivatives of compound 3
The gel tests showed that the diesters of phenyl and naphthyl were very good gelators in EtOH/H₂O=1:1 mixture. However the straight chain alkyl derivatives didn’t behave very well. The following paper from our group further explored structure and gelation relationship. Base on the same head group, terminal alkyne esters and carbamates were synthesized.²⁰,²¹

![Figure 2.1 The structures of different terminal alkyl derivatives](image)

The terminal alkyne behaved much better. Four diesters formed gel in hexane and 6 monoesters formed gel in both water and hexane. The minimum gelation concentrations for 3 compounds were only 3 mg/mL in hexane.

![Figure 2.2 The structures of carbamates compounds](image)
Two carbamate compounds formed gel in water and hexane separately. When we look into the structure of these sugar derivatives, we can draw the following conclusions. The aromatic protection group at 4, 6 positions provide π-π stacking. If there is no functional group at 2, 3 positions, the hydroxyl group will form hydrogen bonding which is proved by X-ray diffraction. When the 2 position was functionalized, there is hydrogen bonding between 3-hydroxyl group and oxygen next to the anomeric position.

To study the structure and gelation relationship, we want to know the effect of the anomeric position methoxyl group. We decided to remove the methoxy group in 3 and this leads to compound 1. We also want to know how α and β conformation affect gelation, so the methoxy group was replaced by a phenoxy group which gave 4, 6-O-benzylidene-β-phenyl-D-glucopyranoside 2.

![Figure 2.3 Structure of compound 1 and 2](image-url)
Results and Discussion

The synthesis of compound 1 followed the method from our previous paper. The head group reacted with acyl chloride to give three products.

To obtain three products in one pot, the acyl chloride was 1.2 equivalents compared with the head group. Some acyl chlorides of R groups were made in situ. Those include 11, 12. The reactions were done in room temperature after around 20 hours. Except naphthyl only gave diester and 2-monoester, all other reactions gave three products. Due to the acyl chloride amount used, the yield of diester (A) product is usually low. The products were purified by flash chromatography. The detailed yields are showed in Table 2.1.
Table 2.1 The yields of three ester products a, b, c.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Total yield</th>
<th>a</th>
<th>b</th>
<th>c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6</td>
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<td>18</td>
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<td></td>
<td>7</td>
<td>64</td>
<td>12</td>
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<td>82</td>
<td>38</td>
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<tr>
<td></td>
<td></td>
<td>9</td>
<td>70</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>59</td>
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<tr>
<td></td>
<td></td>
<td>11</td>
<td>63</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>84</td>
<td>11</td>
</tr>
</tbody>
</table>

The selectivity between 2-monoester and 3-monoester was not significant. The loss of methoxyl group at anomeric position had influenced the selectivity. When there was methoxyl group, 2 position hydroxyl group can form hydrogen bond with methoxyl group and 2 position can be deprotonated more easily. Gel formation was tested in five solvents: water, hexane, ethanol, EtOH/H$_2$O (1: 2) and DMSO/H$_2$O (1: 2). 2 mg sample was added into a small vial followed by 0.1 mL test solvent. Heat was used to solvate the sample if necessary. The vial was cooled to room temperature for about 15 minutes. Then it was inverted to check whether solvent
was held or not. If gel forms, a series of dilution was carried out until gel collapses to find out the minimum gelation concentration. If gel does not form, the status is recorded as soluble, precipitate, insoluble, etc. The gel tests results of compound 1 derivatives are shown in Table 2.2 and 2.3.
Table 2.2 Gelation test results for ester derivatives of 1.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hexane</th>
<th>H₂O</th>
<th>EtOH</th>
<th>EtOH:H₂O (1:2)</th>
<th>DMSO:H₂O (1:2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6A</td>
<td>S</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>6B</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>6C</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>S</td>
<td>P</td>
</tr>
<tr>
<td>7A</td>
<td>S</td>
<td>P</td>
<td>S</td>
<td>S</td>
<td>P</td>
</tr>
<tr>
<td>7B</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>7C</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>8A</td>
<td>S</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>8B</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>8C</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
</tbody>
</table>

All concentrations are in mg/mL; G, gel at room temperature; the numbers after G are minimum gelation concentrations; P, precipitation; S, soluble at~20 mg/mL; the ratios of solvents are in parenthesis.
Table 2.3 Gelation test results for ester derivatives of 1.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hexane</th>
<th>H₂O</th>
<th>EtOH</th>
<th>EtOH:H₂O(1:2)</th>
<th>DMSO:H₂O(1:2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9A</td>
<td>I</td>
<td>P</td>
<td>G 5</td>
<td>P</td>
<td>G5</td>
</tr>
<tr>
<td>9B</td>
<td>I</td>
<td>P</td>
<td>S</td>
<td>G 4</td>
<td>P</td>
</tr>
<tr>
<td>9C</td>
<td>I</td>
<td>P</td>
<td>S</td>
<td>G 10</td>
<td>G 20</td>
</tr>
<tr>
<td>10A</td>
<td>I</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>G 20</td>
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<td>P</td>
<td>S</td>
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<td>11A</td>
<td>S</td>
<td>P</td>
<td>G 7</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>11B</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>11C</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>12A</td>
<td>P</td>
<td>P</td>
<td>G 3</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>12B</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
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<td>12C</td>
<td>P</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
</tbody>
</table>

All concentrations are in mg/mL; G, gel at room temperature; the numbers after G are minimum gelation concentrations; P, precipitation; S, soluble at ~20 mg/mL; the ratios of solvents are in parenthesis.

From the above gelation tests results, we can draw some conclusions. The 5, 6, 7 carbon alkyl group esters did not form any gel. This result was consistent with gelation property of short
chain alkyl esters of 4, 6-\(O\)-benzylidene-methyl-\(\alpha\)-D-glucopyranoside. If the alkyl group is too short, the interaction (van der Waals force) is not strong enough for one dimensional network formation. On the other hand, two of long chain diacetylene esters formed gel in ethanol at 3 mg/mL and 7 mg/mL separately. The aromatic esters are good gelators. Dimer of benzyl ester 9A formed gel at 5 mg/mL in both ethanol and DMSO: H\(_2\)O (1: 2). The 2-isomer of benzyl ester 9B formed gel at 4 mg/mL in EtOH: H\(_2\)O (1: 2). The 3-isomer 9C gelled in EtOH: H\(_2\)O (1: 2), DMSO: H\(_2\)O (1: 2) at 10 mg/mL and 20 mg/mL separately. This result was significantly different from gelation results of benzyl esters of 4, 6-\(O\)-benzylidene-methyl-\(\alpha\)-D-glucopyranoside. In that series, only the dimer of benzyl ester 13 formed gel in EtOH: H\(_2\)O (1: 1) at 7 mg/mL. However the dimer of naphthyl group 13a from that series behaved better than the one in deoxy-glucose series which formed gel in DMSO: H\(_2\)O (1: 2) at 20 mg/mL.

The gel morphology was studied using an Olympus BX60 microscope and a JEOL JSM 5410 scanning electron microscope. The optical images below show that fibers in the gel hold the solvent.\(^{21}\)
Figure 2.5 The image of 9B in EtOH/H_2O (1:2) at 4 mg/mL. The images were taken with gels containing solvents (not dried gels).

Because of diacetylene functional groups in compound 11 and 12, it can be polymerized under UV light or heat. Figure 2.7 shows how polymerization works.

Figure 2.6 The polymerization of diacetylene
The polymerization changes the color of a clear gel to blue. The blue and purple fibers can be seen from Figures 2.7. The SEM image of the zero-gel showed long and thin fibers.

Figure 2.7 Optical micrographs under bright field (a, b) and scanning electron micrograph (c) of the gel formed by compound 12A in ethanol after exposure to UV light for 3 min.

Figure 2.8 Scanning electron micrograph (c) of the gel formed by compound 12A in ethanol after exposure to UV light for 3 min.
From the functionalization of 4, 6-\(O\)-benzylidene-methyl-\(\alpha\)-D-glucopyranoside 3 and 4, 6-\(O\)-benzylidene-deoxy-\(\alpha\)-D-glucopyranoside 1, we learned that the terminal alkynes esters, aromatic esters, long chain diacetylenes are very good functional groups for gelators. To further explore the gelators structures and understand the influence of the anomeric substituents we studied sugar head group 4, 6-\(O\)-benzylidene-\(\beta\)-phenyl-D-glucopyranoside 2, which is commercially available. We decided to use terminal alkynes esters and long chain diacetylenes. We didn’t synthesized aromatic esters, because two aromatic groups are enough for \(\pi\)-\(\pi\) stacking. The structures of functional groups are shown below. All the acyl chlorides (14, 15, 16, 17, 18) are made in situ. In these reactions, only two products were obtained. There is no 3-monoester product. The yields are shown in the Table 2.4. The gel tests results are shown in the Table 2.5.

```
\text{Scheme 2.3 Synthesis of esters LMOGs of compound 2}
```
Table 2.4 The yields of ester a, b of compound 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>Total yields</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
<td>b</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>75 %</td>
<td>30 %</td>
<td>45 %</td>
</tr>
<tr>
<td>15</td>
<td>83 %</td>
<td>20 %</td>
<td>63 %</td>
</tr>
<tr>
<td>16</td>
<td>72 %</td>
<td>30 %</td>
<td>42 %</td>
</tr>
<tr>
<td>17</td>
<td>68 %</td>
<td>5 %</td>
<td>63 %</td>
</tr>
<tr>
<td>18</td>
<td>69 %</td>
<td>4 %</td>
<td>65 %</td>
</tr>
</tbody>
</table>

In this series, no 3-monoester was obtained in the reaction. The possible explanation is β-phenoxy group is an electron withdrawing group which makes 2 position hydroxyl group easier to lose hydrogen and attack acyl chloride. After the 2-position was activated, 3-position was easier to be approached. That is why some reactions produced fair amount of diesters.
Table 2.5 Gelation test results of for ester derivatives of 2.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hexane</th>
<th>H$_2$O</th>
<th>EtOH</th>
<th>EtOH: H$_2$O (1:2)</th>
<th>DMSO: H$_2$O (1:2)</th>
<th>iPrOH</th>
<th>Toluene</th>
<th>EtOH: H$_2$O (1:1)</th>
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<tbody>
<tr>
<td>14A</td>
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<td>P</td>
<td>S</td>
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<td>P</td>
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<td>S</td>
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<tr>
<td>14B</td>
<td>I</td>
<td>P</td>
<td>S</td>
<td>G 7</td>
<td>G 7</td>
<td>S</td>
<td>S</td>
<td>G 20</td>
</tr>
<tr>
<td>15A</td>
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<td>S</td>
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<td>16A</td>
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All concentrations are in mg/mL; G, gel at room temperature; the numbers after G are minimum gelation concentrations; P, precipitation; S, soluble at~20 mg/mL; the ratios of solvents are in parenthesis.

Terminal alkyne esters had similar gelation property compared with alkyne esters of 4, 6-"O-benzylidene-methyl-α-D-glucopyranoside. The 2-monoester of 5 carbon terminal alkyne
ester 14B formed gel at 7 mg/mL in both EtOH: H₂O (1: 2) and DMSO: H₂O (1: 2). 2-monoester of 6 carbon alkyne ester 15B formed gel in EtOH: H₂O (1: 2) at 5 mg/mL. 2-monoester of 7 carbon terminal alkyne ester 16B behaved best and gelled EtOH: H₂O (1: 2) at 3 mg/mL. It seemed that gelation improved as the chain length of terminal alkynes increased. The four esters of long chain diacetylene 17A, 17B, 18A, 18B did not form any gel. The phenyl group at anomeric position might affect the gelation tendency of these long chain lipids.

The gels formed by these compounds were characterized with optical micrographs, as shown in Figures 2.9-2.113. Typically they form fibers as shown in Figure 2.10 and 2.11. But it also depended on the compounds. For example, compound 15B formed flower like structures with short tubes. On the other hand, compound 14B formed sheets, and if we look closer, we can see the sheet was made by tubes packing together.

Figure 2.9 500x Optical micrographs of gel formed by Compound 15B at 5mg/mL in DMSO/H₂O (1: 2).
Figure 2.10  200x Optical micrographs of gel formed by compound 14B at 6.7mg/mL in DMSO/H_2O (1: 2).

Figure 2.11  500x Optical micrographs of gel formed by Compound 14B at 6.7mg/mL in DMSO/H_2O (1: 2).
Figure 2.12 200x Optical micrographs of gel formed by compound 14B at 6.7mg/mL in EtOH/H₂O (1: 2).

Figure 2.13 500x Optical micrographs of gel formed by Compound 14B at 6.7mg/mL in EtOH/H₂O (1: 2).
Conclusion

We systematically studied the ester functional groups at 2, 3 positions in different sugar derivatives 1, 2, 3. The ester functional groups include aromatic groups, straight chain alkyls, terminal alkynes, and long chain diacetylenes.

![Chemical structures](image)

The gelation tests showed that esters of terminal alkynes usually formed gel in different solvents like water, ethanol, EtOH: H₂O (1:2) and DMSO: H₂O (1: 2). On the other hand, straight chain alkyl esters didn’t behave well. The aromatic functional groups are phenyl and naphthyl groups. Their esters were very good gelators. The minimum gelation concentration reached 4 mg/mL. The long chain diacetylene esters of compound 2 were very good gelators in ethanol.

In the design of gelators, the balance of different interactions was critical. Even if the chain length was the same, the terminal alkyne esters were much better gelators than alkyl esters. The alkyne chain was more rigid, which was easier for molecular packing. The aromatic groups usually could provide π-π stacking. However if π-π stacking and van der Waals forces were too much, it would lead to precipitation. This could be seen in the diacetylene dimer of compound 2. The hydrogen bonding was not very critical among these esters. The common one was the hydrogen bonding between 2 or 3 position hydroxyl group and the oxygen next to the anomeric carbon.
Experimental section

Materials and Instruments: General chemicals and reagents were purchased from Aldrich, or VWR. The diacetylene containing fatty acids were purchased from GFS chemicals. Optical microscope images were recorded with an Olympus BX60 microscope and CCD camera. NMR spectra were recorded using a 400 MHz Varian NMR spectrometer. High resolution mass spectrometry data were measured on the Q-Tof of the Mass Spectrometry lab at the University of Illinois after the low resolution masses were confirmed. The ionization technique used was ESI (electrospray ionization). Melting points were measured using a Fisher-Jones melting point apparatus.

Optical microscopy. The sample was prepared as a small piece of gel placed on a clean microscope glass slide, and the gel was imaged directly under the microscope. The program used to acquire and store the photos was Corel Photo-Paint 7.

Scanning electron microscopy. A piece of the gel was deposited on an aluminum sample holder and allowed to dry in a desiccator. The dried gel sample was coated with a thin layer of platinum (~100–150 Å) by a Denton Vacuum (model Desk II) at a reduced pressure of ~30 mTorr and a current of 45 mA for 60 sec. The sample was analyzed using a JEOL JSM 5410 scanning electron microscope with an EDAX Detecting Unit PV9757/05 ME (Model 204B+, active area = 10 mm²).
**General procedure for ester synthesis:**

Sugar head group (80-100 mg) was mixed with 5 molar equivalents of anhydrous pyridine in 2 mL DCM/THF. The mixture was stirred and cooled in ice bath. 1.2 molar equivalents of acyl chloride were added dropwise. Then the mixture was left at room temperature for 15-20 hours. A NMR sample was taken to confirm that reaction was done. The common workup procedure was to dilute the reaction mixture with about 5 mL water followed by extraction with DCM (3x 10mL). The DCM phase was combined and dried with sodium sulfate. The crude product was purified by flash chromatography.

**Compound 6A** (30 mg, 18%), white solid, mp 71.0–72.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.40–7.46 (m, 2H), 7.32–7.37 (m, 3H), 5.50 (s, 1H), 5.36 (t, 1H, $J = 9.5$ Hz), 5.05 (m, 1H), 4.34 (dd, 1H, $J = 4.9$, 10.5 Hz), 4.12 (dd, 1H, $J = 5.9$, 11.0 Hz), 3.72 (t, 1H, $J = 10.3$ Hz), 3.63 (t, 1H, $J = 9.5$ Hz), 3.47 (dt, 1H, $J = 4.8$, 9.5, 9.9 Hz), 3.39 (t, 1H, $J = 10.8$ Hz), 2.26–2.34 (m, 4H), 1.52–1.64 (m, 4H), 1.23–1.38 (m, 4H), 0.90 (t, 3H, $J = 7.3$ Hz), 0.94 (t, 3H, $J = 7.3$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 172.8, 136.9, 129.0, 128.2, 126.0, 101.3, 78.9, 72.0, 71.4 69.3, 68.6, 67.5, 33.9, 33.7, 27.0, 26.8, 22.1, 22.0, 13.6. HRMS Calcd for $C_{23}H_{33}O_7$ [M + H]$^+$ 420.2226, found 421.2217.

**Compound 6B** (42 mg, 32%); white solid; 107.0–109.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.47–7.52 (m, 2H), 7.35–7.41 (m, 3H), 5.55 (s, 1H), 4.95 (ddd, 1H, $J = 5.9$, 9.2, 10.6 Hz), 4.33 (dd, 1H, $J = 5.1$, 10.6 Hz), 4.12 (dd, 1H, $J = 5.9$, 11.0 Hz), 3.92 (t, 1H, $J = 9.2$ Hz), 3.71 (t, 1H, $J = 10.3$ Hz), 3.55 (t, 1H, $J = 9.2$ Hz), 3.40 (dt, 1H, $J = 4.8$, 9.5 Hz), 3.30 (t, 1H, $J =
10.8 Hz), 2.62 (s, 1H), 2.37 (m, 2H), 1.62 (m, 2H), 1.36 (m, 2H), 0.92 (t, 3H, \( J = 7.3 \) Hz). \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 173.4, 136.9, 129.3, 128.4, 126.3, 101.9, 81.2, 72.9, 71.5, 71.0, 68.7, 67.3, 33.8, 26.9, 22.1, 13.7. HRMS Calcd for C\(_{13}\)H\(_{25}\)O\(_6\) [M + H]\(^+\) 337.1651, found 337.1644.

Compound 6C (31 mg, 23%); white solid; mp 72.0–74.0 °C. \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.42–7.48 (m, 2H), 7.33–7.38 (m, 3H), 5.51 (s, 1H), 5.00 (t, 1H, \( J = 9.2 \) Hz), 4.35 (dd, 1H, \( J = 4.8, 10.6 \) Hz), 4.11 (dd, 1H, \( J = 5.9, 11.4 \) Hz), 3.83 (m, 1H), 3.70 (t, 1H, \( J = 10.3 \) Hz), 3.61 (t, 1H, \( J = 9.3 \) Hz), 3.44 (dt, 1H, \( J = 4.8, 9.9 \) Hz), 3.39 (t, 1H, \( J = 11.0 \) Hz), 2.95 (d, 1H, \( J = 4.4 \) Hz), 2.41 (t, 2H, \( J = 7.5 \) Hz), 1.63 (pentet, 2H, \( J = 7.5 \) Hz), 1.34 (hex, 2H, \( J = 7.5 \) Hz), 0.87 (t, 3H, \( J = 7.5 \) Hz). \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 175.7, 136.9, 129.1, 128.2, 126.1, 101.4, 78.4, 77.1, 71.4, 70.6, 70.1, 68.8, 34.1, 27.0, 22.1, 13.6. HRMS Calcd for C\(_{18}\)H\(_{25}\)O\(_6\) [M + H]\(^+\) 337.1651, found 337.1646.

Compound 7A (22 mg, 12%); white solid; mp 37.0–38.0 °C. \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.40–7.46 (m, 2H), 7.32–7.38 (m, 3H), 5.50 (s, 1H), 5.36 (t, 1H, \( J = 9.5 \) Hz), 5.05 (dd~dt, 1H, \( J = 5.9, 9.5, 10.3 \) Hz), 4.34 (dd, 1H, \( J = 4.9, 10.5 \) Hz), 4.12 (dd, 1H, \( J = 5.9, 11.2 \) Hz), 3.72 (t, 1H, \( J = 10.3 \) Hz), 3.63 (t, 1H, \( J = 9.5 \) Hz), 3.47 (dt, 1H, \( J = 5.1, 9.9 \) Hz), 3.39 (t, 1H, \( J = 10.8 \) Hz), 2.25–2.37 (m, 4H), 1.53–1.64 (m, 4H), 1.20–1.36 (m, 8H), 0.89 (t, 3H, \( J = 7.0 \) Hz), 0.82 (t, 3H, \( J = 7.0 \) Hz). \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 172.8, 136.9, 129.0, 128.2, 126.0, 101.4, 78.9, 72.0, 71.5, 69.4, 68.6, 67.5, 34.3, 34.0, 31.15, 31.1, 24.7, 24.5, 22.2, 13.9, 13.8. HRMS Calcd for C\(_{25}\)H\(_{37}\)O\(_7\) [M + H]\(^+\) 449.2539, found 449.2538.
Compound **7B** (44 mg, 32%); white solid; mp 112.0–114.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.46–7.53 (m, 2H), 7.35–7.42 (m, 3H), 5.55 (s, 1H), 4.95 (m, 1H), 4.33 (dd, 1H, $J = 4.8$, 10.6 Hz), 4.12 (dd, 1H, $J = 5.7$, 11.2 Hz), 3.91 (t, 1H, $J = 9.2$ Hz), 3.71 (t, 1H, $J = 10.3$ Hz), 3.54 (t, 1H, $J = 9.3$ Hz), 3.40 (dt, 1H, $J = 4.8$, 9.5 Hz), 3.30 (t, 1H, $J = 10.8$ Hz), 2.64 (s, 1H), 2.36 (m, 2H), 1.64 (p, 2H, $J = 7.3$ Hz), 1.31 (m, 4H), 0.90 (t, 3H, $J = 6.8$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 173.4, 136.9, 129.3, 128.3, 126.2, 101.9, 81.2, 72.8, 71.5, 71.0, 68.7, 67.3, 34.1, 31.2, 24.5, 22.3, 13.9. HRMS Calcd for C$_{19}$H$_{27}$O$_6$ [M + H]$^+$ 351.1808, found 351.1801.

Compound **7C** (27 mg, 20%); white solid; mp 113.0–114.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.42–7.48 (m, 2H), 7.33–7.39 (m, 3H), 5.51 (s, 1H), 5.01 (t, 1H, $J = 9.2$ Hz), 4.35 (dd, 1H, $J = 4.9$, 10.5 Hz), 4.11 (dd, 1H, $J = 5.7$, 11.5 Hz), 3.83 (m, 1H), 3.70 (t, 1H, $J = 10.3$ Hz), 3.61 (t, 1H, $J = 9.5$ Hz), 3.44 (dt, 1H, $J = 4.8$, 9.9 Hz), 3.39 (t, 1H, $J = 10.8$ Hz), 2.98 (sb, 1H), 2.40 (t, 2H, $J = 7.3$ Hz), 1.65 (m, 2H), 1.22–1.36 (m, 4H), 0.84 (t, 3H, $J = 7.0$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 175.7, 137.0, 129.1, 128.2, 126.1, 101.4, 78.4, 77.1, 71.4, 70.6, 70.1, 68.8, 34.3, 31.1, 24.7, 22.2, 13.8 HRMS Calcd for C$_{19}$H$_{27}$O$_6$ [M + H]$^+$ 351.1808, found 351.1801.

Compound **8A** (72 mg, 38%); white solid; mp 49.0–50.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.40–7.46 (m, 2H), 7.32–7.38 (m, 3H), 5.49 (s, 1H), 5.36 (t, 1H, $J = 9.5$ Hz), 5.05 (ddd, 1H, $J = 5.9$, 9.5, 10.3 Hz), 4.34 (dd, 1H, $J = 4.9$, 10.5 Hz), 4.12 (dd, 1H, $J = 5.9$, 11.0 Hz), 3.71 (t, 1H, $J = 10.3$ Hz), 3.63 (t, 1H, $J = 9.5$ Hz), 3.47 (dt, 1H, $J = 4.8$, 9.9 Hz), 3.38 (t, 1H,
$J = 11.0$ Hz), 2.24–2.37 (m, 4H), 1.53–1.64 (m, 4H), 1.17–1.36 (m, 12H), 0.88 (t, 3H, $J = 7.0$ Hz), 0.84 (t, 3H, $J = 7.0$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 172.79, 172.76, 136.9, 128.9, 128.1, 126.0, 101.3, 78.8, 72.0, 71.4, 69.3, 68.6, 67.4, 34.2, 34.0, 31.4, 31.3, 28.64, 28.60, 24.9, 24.7, 22.4, 22.3, 14.0. HRMS Calcd for C$_{27}$H$_{41}$O$_7$ [M + H]$^+$ 477.2852, found 477.2847.

Compound 8B (33 mg, 23%); white solid; mp 102.0–104.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.46–7.53 (m, 2H), 7.35–7.42 (m, 3H), 5.55 (s, 1H), 4.95 (ddd, 1H, $J = 5.9, 9.2, 10.3$ Hz), 4.34 (dd, 1H, $J = 5.1, 10.6$ Hz), 4.12 (dd, 1H, $J = 5.9, 11.0$ Hz), 3.92 (t, 1H, $J = 9.2$ Hz), 3.71 (t, 1H, $J = 10.3$ Hz), 3.55 (t, 1H, $J = 9.2$ Hz), 3.40 (dt, 1H, $J = 5.0, 9.7$ Hz), 3.30 (t, 1H, $J = 10.8$ Hz), 2.65 (sb, 1H), 2.36 (m, 2H), 1.63 (p, 2H, $J = 7.3$ Hz), 1.24–1.39 (m, 6H), 0.88 (t, 3H, $J = 6.8$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 173.4, 136.9, 129.3, 128.3, 126.2, 101.9, 81.2, 72.8, 71.5, 71.0, 68.7, 67.3, 34.1, 31.4, 28.7, 24.8, 22.4, 14.0; HRMS Calcd for C$_{20}$H$_{29}$O$_6$ [M + H]$^+$ 365.1964, found 365.1958.

Compound 8C (30 mg, 21%); white solid; mp 89.0–91.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.42–7.49 (m, 2H), 7.32–7.40 (m, 3H), 5.51 (s, 1H), 5.01 (t, 1H, $J = 9.2$ Hz), 4.35 (dd, 1H, $J = 4.9, 10.6$ Hz), 4.11 (dd, 1H, $J = 5.9, 11.4$ Hz), 3.83 (m, 1H), 3.71 (t, 1H, $J = 10.3$ Hz), 3.61 (t, 1H, $J = 9.3$ Hz), 3.44 (dt, 1H, $J = 4.9, 9.9$ Hz), 3.39 (t, 1H, $J = 11.0$ Hz), 2.97 (sb, 1H), 2.41 (t, 2H, $J = 7.5$ Hz), 1.64 (p, 2H, $J = 7.3$ Hz), 1.15–1.36 (m, 6H), 0.84 (t, 3H, $J = 6.6$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 175.7, 137.0, 129.1, 128.2, 126.1, 101.4, 78.4, 77.1, 71.4, 70.6, 70.1, 68.8, 34.4, 31.4, 28.6, 25.0, 22.4, 14.0; HRMS Calcd for C$_{20}$H$_{29}$O$_6$ [M + H]$^+$ 365.1964, found 365.1953.
Compound 9A (14 mg, 8%); white solid; mp 162.0–163.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.94–8.03 (m, 4H), 7.47–7.55 (m, 2H), 7.35–7.45 (m, 6H), 7.29–7.34 (m, 3H), 5.83 (t, 1H, $J = 9.5$ Hz), 5.56 (s, 1H), 5.40 (m, 1H), 4.42 (dd, 1H, $J = 4.9, 10.5$ Hz), 4.38 (dt, 1H, $J = 4.8, 9.7$ Hz), 3.89 (t, 1H, $J = 9.5$ Hz), 3.81 (t, 1H, $J = 10.3$ Hz), 3.61 (t, 1H, $J = 9.3$ Hz), 3.63 (dt, 1H, $J = 4.9, 9.9$ Hz), 3.58 (t, 1H, $J = 10.8$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 165.8, 165.7, 136.8, 133.4, 133.1, 129.8, 129.76, 129.6, 129.0, 128.5, 128.3, 128.2, 126.1, 101.5, 79.1, 72.7, 71.7, 70.5, 68.7, 67.7; HRMS Calcd for C$_{27}$H$_{25}$O$_7$ [M + H]$^+$ 460.1600, found 461.1589.

Compound 9B (26 mg, 19%); white solid; mp 126.0–127.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.05 (d, 2H, $J = 7.1$ Hz), 7.60–7.37 (m, 8H), 5.57 (s, 1H), 5.19 (ddd, 1H, $J = 10.6, 9.2, 5.9$ Hz), 4.36 (dd, 1H, $J = 10.3, 5.0$ Hz), 4.26 (dd, 1H, $J = 11.0, 5.9$ Hz), 4.08 (t, 1H, $J = 9.2$ Hz), 3.75 (t, 1H, $J = 10.3$ Hz), 3.61 (dd~t, 1H, $J = 9.5, 9.2$ Hz), 3.45 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100MHz) $\delta$ (ppm) 166.0, 136.9, 133.3, 129.7, 129.3, 129.2, 128.4, 128.3, 126.3, 101.8, 81.1, 72.6, 72.1, 71.0, 68.5, 67.2.

Compound 9C (45 mg, 32%); white solid; mp 155.0–156.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.08 (d, 2H, $J = 7.7$ Hz), 7.58 (m, 1H), 7.41–7.50 (m, 4H), 7.30–7.37 (m, 3H), 5.56 (s, 1H), 5.30 (t, 1H, $J = 9.5$ Hz), 4.38 (dd, 1H, $J = 4.9, 10.5$ Hz), 4.15 (dd, 1H, $J = 5.9, 11.4$ Hz), 3.98 (ddd, 1H, $J = 5.9, 9.2, 10.5$ Hz), 3.72–3.81 (m, 2H), 3.51 (dt, 1H, $J = 4.9, 9.5$ Hz), 3.46 (t, 1H, $J = 11.0$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 167.9, 136.9, 133.5, 129.9, 129.4,
129.0, 128.4, 128.2, 126.0, 101.4, 78.6, 77.8, 71.4, 70.6, 70.0, 68.8. HRMS Calcd for C_{20}H_{21}O_{6}\ [M + H]^+ 357.1338, found 357.1329.

Compound 10A (71 mg, 33%); white solid; mp 135.0–137.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.87 (d, 1H, $J = 8.4$ Hz), 8.68 (d, 1H, $J = 8.4$ Hz), 8.26 (m, 1H, $J = 7.3$ Hz), 8.06 (d, 1H, $J = 7.3$ Hz), 8.01 (d, 1H, $J = 8.1$ Hz), 7.95 (d, 1H, $J = 8.1$ Hz), 7.79–7.87 (m, 2H), 7.37–7.57 (m, 8H), 7.31–7.37 (m, 3H), 6.00 (t, 1H, $J = 9.5$ Hz), 5.63 (s, 1H), 5.60 (m, 1H), 4.47 (m, 2H), 3.97 (t, 1H, $J = 9.5$ Hz), 3.85 (t, 1H, $J = 10.3$ Hz), 3.66–3.75 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 167.0, 166.2, 136.9, 134.1, 133.7, 133.6, 133.1, 131.4, 131.0, 130.9, 129.4, 129.0, 128.6, 128.4, 128.0, 127.6, 126.3, 126.2, 126.1, 125.54, 125.46, 124.54, 124.48, 101.5, 79.2, 73.0, 71.8, 70.2, 68.7, 67.9. HRMS Calcd for C_{35}H_{29}O_{7} [M + H]^+ 561.1913, found 561.1918.

Compound 10B (59 mg, 37%); white solid; mp 93.0–95.0 °C. $^1$H NMR (CDCl$_3$, 400MHz) δ (ppm) 8.91 (d, 1H, $J = 8.8$ Hz), 8.21 (d, 1H, $J = 7.3$ Hz), 8.05 (d, 1H, $J = 8.4$ Hz), 7.89 (d, 1H, $J = 8.1$ Hz), 7.63 (m, 1H), 7.48–7.58 (m, 4H), 7.35–7.43 (m, 3H), 5.58 (s, 1H), 5.30 (m, 1H), 4.37 (m, 2H), 4.13 (dt, 1H, $J = 2.6, 9.2$ Hz), 3.76 (t, 1H, $J = 10.3$ Hz), 3.64 (t, 1H, $J = 9.2$ Hz), 3.42–3.54 (m, 2H), 2.83 (d, 1H, $J = 2.6$Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ (ppm) 166.9, 137.0, 133.8, 133.9, 131.3, 130.5, 129.3, 129.0, 128.4, 128.0, 126.4, 126.3, 125.7, 124.4, 102.0, 81.3, 72.9, 72.2, 71.1, 68.7, 67.4. HRMS Calcd for C_{24}H_{23}O_{6} [M + H]^+ 407.1495, found 407.1491.
**General procedure for acyl chloride synthesis**

For compound **11, 12, 14, 15, 16, 17, 18**, the acyl chlorides were not commercially available, so the acids were used to synthesize acyl chloride *in situ*.

For compound **11**: 8, 10-heneicosadiynoic acid (166 mg, 5.2 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.1 mL, 12 mmol) was added to mixture slowly and the mixture was stirred at room temperature for 2 hours at which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of ester synthesis.

Compound **11A** (20 mg, 6%); white solid; 45.0–47.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40–7.45 (m, 2H), 7.32–7.37 (m, 3H), 5.50 (s, 1H), 5.35 (t, 1H, $J = 9.5$ Hz), 5.05 (ddd-dt, 1H, $J = 5.9$, 9.5, 10.3 Hz), 4.34 (dd, 1H, $J = 4.9$, 10.5 Hz), 4.12 (dd, 1H, $J = 5.9$, 11.0 Hz), 3.72 (t, 1H, $J = 10.3$ Hz), 3.63 (t, 1H, $J = 9.5$ Hz), 3.47 (dt, 1H, $J = 5.1$, 9.7 Hz), 3.38 (t, 1H, $J = 10.8$ Hz), 2.14–2.37 (m, 12H), 1.58 (m, 4H), 1.41 (m, 8H), 1.38 (m, 4H), 1.26 (s, 32H), 0.88 (t, 6H, $J = 6.8$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 172.71, 172.65, 136.8, 129.1, 128.2, 101.4, 78.9, 77.7, 77.6, 77.2, 77.1, 72.1, 71.4, 69.4, 68.6, 67.5, 65.5, 65.4, 65.2, 65.1, 34.2, 33.9, 31.9, 29.6, 29.5, 29.3, 29.1, 28.9, 28.5, 28.3, 28.1, 28.0, 24.9, 24.6, 22.7, 19.2, 19.1, 14.1. HRMS Calcd for C$_{55}$H$_{80}$O$_7$Na [M + Na]$^+$ 875.5802, found 875.5773.

Compound **11B** (70 mg, 33%); white solid; mp 73.0–75.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45–7.52 (m, 2H), 7.33–7.41 (m, 3H), 5.55 (s, 1H), 4.95 (ddd, 1H, $J = 5.9$, 9.2, 10.6 Hz), 4.34 (dd, 1H, $J = 4.5$, 10.5 Hz), 4.12 (dd, 1H, $J = 5.9$, 11.0 Hz), 3.92 (t, 1H, $J = 9.2$ Hz), 3.71 (t, 1H, $J = 10.3$ Hz), 3.55 (t, 1H, $J = 9.3$ Hz), 3.40 (dt, 1H, $J = 4.8$, 9.7 Hz), 3.30 (t, 1H, $J =
10.8 Hz), 2.29–2.43 (m, 2H), 2.20–2.29 (m, 4H), 1.64 (p, 2H $J = 7.3$ Hz), 1.51 (m, 4H), 1.32–1.45 (m, 2H), 1.26 (sb, 16H), 0.88 (t, 3H, $J = 6.8$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 173.2, 136.9, 129.3, 128.3, 126.2, 101.9, 81.2, 77.7, 77.1, 72.9, 71.5, 71.0, 68.7, 67.3, 65.4, 65.2, 34.0, 31.9, 29.5, 29.4, 29.3, 29.1, 28.8, 28.5, 28.4, 28.3, 28.1, 24.7, 24.5, 22.7, 19.2, 19.1, 14.1. HRMS Calcd for C$_{34}$H$_{48}$O$_6$Na$[M + Na]^+$ 573.3349, found 575.3344.

Compound 11C (52 mg, 24%); white solid; mp 58.0–59.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42–7.47 (m, 2H), 7.32–7.39 (m, 3H), 5.51 (s, 1H), 5.02 (t, 1H, $J = 9.2$ Hz), 4.34 (dd, 1H, $J = 4.9$, 10.5 Hz), 4.10 (dd, 1H, $J = 5.7$, 11.5 Hz), 3.83 (ddd, 1H, $J = 5.9$, 9.2, 10.6 Hz), 3.70 (t, 1H, $J = 10.3$ Hz), 3.60 (t, 1H, $J = 9.5$ Hz), 3.44 (td, 1H, $J = 4.8$, 9.7 Hz), 3.39 (t, 1H, $J = 10.8$ Hz), 2.89 (sbr, 1H), 2.40 (t, 2H, $J = 7.3$ Hz), 2.24 (t, 2H, $J = 7.0$ Hz), 2.18 (t, 2H, $J = 6.8$ Hz), 1.64 (p, 2H, $J = 7.3$ Hz), 1.51 (p, 2H, $J = 7.3$ Hz), 1.19–1.45 (m, 20H), 0.88 (t, 3H, $J = 6.8$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 175.4, 137.0, 129.1, 128.2, 126.1, 101.5, 78.4, 77.7, 77.2, 77.0, 71.4, 70.6, 70.0, 68.8, 65.4, 65.2, 34.2, 31.8, 29.5, 29.4, 29.3, 29.0 28.8, 28.3, 27.9, 24.8, 22.6, 19.2, 19.0, 14.1. HRMS Calcd for C$_{34}$H$_{48}$O$_6$Na$[M + Na]^+$ 573.3349, found 575.3336.

For compound 12: 10,12-tricosadiynoic acid (180 mg, 0.52 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.1 mL, 1.2 mmol) was added to mixture slowly and the mixture was stirred at room temperature for 2 hours at which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of ester synthesis.
Compound 12A (40 mg, 11%); white solid; mp 55.0–57.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40–7.45 (m, 2H), 7.32–7.37 (m, 3H), 5.50 (s, 1H), 5.35 (t, 1H, $J = 9.5$ Hz), 5.04 (ddd-dt, 1H, $J = 5.9, 9.9, 10.3$ Hz), 4.33 (dd, 1H, $J = 4.9, 10.3$ Hz), 4.12 (dd, 1H, $J = 5.9, 11.0$ Hz), 3.72 (t, 1H, $J = 10.3$ Hz), 3.63 (dd-t, 1H, $J = 9.2, 9.9$ Hz), 3.47 (dt, 1H, $J = 5.1, 9.5$ Hz), 3.38 (t, 1H, $J = 10.8$ Hz), 2.17–2.35 (m, 12H), 1.41–1.61 (m, 12H), 1.14–1.40 (m, 44H), 0.88 (t, 6H, $J = 7.0$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 172.81, 172.76, 136.9, 129.0, 128.2, 126.0, 101.4, 78.9, 77.6, 77.4, 71.5, 69.4, 68.6, 67.5, 65.3, 65.2, 34.2, 34.0, 31.8, 29.5, 29.4, 29.3, 29.0, 28.9, 28.8, 28.7, 28.3, 28.2, 25.0, 24.7, 22.6, 19.1, 14.1. HRMS Calcd for C$_{59}$H$_{88}$O$_7$Na $[M + Na]^+$ 931.6428, found 931.6392.

Compound 12B (105 mg, 46%); white solid; mp 88.0–90.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45–7.51 (m, 2H), 7.33–7.41 (m, 3H), 5.55 (s, 1H), 4.95 (ddd, 1H, $J = 5.9, 9.2, 10.6$ Hz), 4.33 (dd, 1H, $J = 5.1, 10.6$ Hz), 4.12 (dd, 1H, $J = 5.9, 11.0$ Hz), 3.91 (t, 1H, $J = 9.2$ Hz), 3.71 (t, 1H, $J = 10.3$ Hz ), 3.54 (t, 1H, $J = 9.2$ Hz), 3.40 (dt, 1H, $J = 4.9, 9.7$ Hz), 3.30 (t, 1H, $J = 10.8$ Hz), 2.29–2.42 (m, 2H), 2.24 (t, 4H, $J = 6.8$ Hz), 1.63 (m, 2H), 1.52 (p, 4H, $J = 7.3$ Hz), 1.17–1.43 (m, 22H), 0.88 (t, 3H, $J = 6.8$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 172.3, 136.9, 129.3, 128.3, 126.2, 101.9, 81.2, 77.6, 77.4, 72.8, 71.5, 71.0, 68.6, 67.3, 65.3, 65.2, 34.1, 31.9, 29.54, 29.46, 29.3, 29.1, 28.9, 28.85, 28.7, 28.32, 28.26, 24.8, 22.7, 19.2, 14.1. HRMS Calcd for C$_{36}$H$_{52}$O$_6$Na $[M + Na]^+$ 603.3662, found 603.3657.

Compound 12C (61 mg, 27%); white solid; mp 41.0–43.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42–7.47 (m, 2H), 7.32–7.38 (m, 3H), 5.50 (s, 1H), 5.03 (t, 1H, $J = 9.2$ Hz), 4.33 (dd,
1H, J = 4.9, 10.5 Hz), 4.09 (dd, 1H, J = 4.8, 9.5 Hz), 3.82 (m, 1H), 3.70 (t, 1H, J = 10.3 Hz), 3.59 (t, 1H, J = 9.5 Hz), 3.44 (td, 1H, J = 4.8, 9.5 Hz), 3.38 (t, 1H, J = 10.8 Hz), 2.40 (t, 2H, J = 7.5 Hz), 2.16–2.30 (m, 4H), 1.63 (m, 2H), 1.42–1.56 (m, 4H), 1.17–1.43 (m, 22H), 0.88 (t, 3H, J = 7.0 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 175.5, 137.0, 129.1, 128.2, 126.1, 101.4, 78.4, 77.6, 77.4, 76.9, 71.3, 70.6, 70.0, 68.7, 65.3, 65.2, 34.3, 31.8, 29.5, 29.4, 29.3, 29.0 (2), 28.8, 28.75, 28.7, 28.3, 28.2, 24.9, 22.6, 19.2, 19.1, 14.1. HRMS Calcd for C$_{36}$H$_{52}$O$_6$Na [M + Na]$^+$ 603.3662, found 603.3656.

For compound 14: 4-pentynoic acid (100 mg, 1 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.1 mL, 1.2 mmol) was added to mixture slowly and followed by 1 drop anhydrous DMF. The mixture was stirred at room temperature for 2 hours at which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of ester synthesis.

Compound 14A (31 mg, 30%); light yellow solid; mp 115.0-116.0°C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49 – 7.39 (m, 2H), 7.34 (ddd, J = 20.8, 11.2, 5.5, 4H), 7.08 (t, J = 7.4, 2H), 6.99 (d, J = 7.8, 2H), 5.53 (s, 1H), 5.45 (t, J = 9.4, 1H), 5.36 – 5.29 (m, 1H), 5.20 (d, J = 7.7, 1H), 4.42 (dd, J = 10.6, 4.9, 1H), 3.84 (ddd, J = 19.3, 9.8, 2H), 3.68 (td, J = 9.7, 4.9, 1H), 2.66 – 2.37 (m, 8H), 1.91 (dt, J = 10.0, 2.5, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.8, 170.3, 136.6, 129.6, 129.2, 128.2, 126.2, 123.5, 117.0, 101.6, 99.6, 82.2, 78.1, 72.2, 71.8, 69.3, 69.2, 68.5, 66.6, 33.2, 33.1, 14.3, 14.2. HRMS Calcd for C$_{29}$H$_{29}$O$_8$ [M + H]$^+$ 505.1862, found 505.1865.
Compound 14B (39 mg, 45%); white solid; mp 54.0-55.0 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.45 (dd, J = 6.7, 2.9, 2H), 7.41 – 7.28 (m, 5H), 7.14 – 6.99 (m, 3H), 5.52 (s, 1H), 5.35 (t, J = 9.4, 1H), 5.11 (d, J = 7.6, 1H), 4.39 (dd, J = 10.5, 4.8, 1H), 3.94 – 3.71 (m, 3H), 3.66 (td, J = 9.7, 4.9, 1H), 2.67 (dd, J = 11.2, 4.2, 2H), 2.54 (ddd, J = 9.4, 5.8, 2.2, 2H), 1.91 (t, J = 2.6, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 171.6, 156.8, 136.8, 129.7, 129.2, 128.3, 126.2, 123.4, 117.0, 101.6, 101.5, 82.3, 78.1, 73.9, 73.1, 69.2, 68.6, 66.6, 33.4, 14.5. HRMS Calcd for C₂₄H₂₄O₇Na [M + Na]⁺ 447.1420, found 447.1418.

For compound 15: 5-hexynoic acid (0.11 mL, 1 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.1 mL, 1.2 mmol) was added to mixture slowly and followed by 1 drop anhydrous DMF. The mixture was stirred at room temperature for 2 hours at which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of ester synthesis.

Compound 15A (22 mg, 20%); white solid; mp 68.0-70.0 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.44 (dd, J = 6.5, 2.9, 2H), 7.40 – 7.27 (m, 5H), 7.08 (t, J = 7.4, 1H), 7.00 (d, J = 7.9, 2H), 5.54 (s, 1H), 5.43 (t, J = 9.4, 1H), 5.34 – 5.28 (m, 1H), 5.19 (d, J = 7.7, 1H), 4.42 (dd, J = 10.5, 4.9, 1H), 3.90 – 3.77 (m, 2H), 3.67 (td, J = 9.6, 4.9, 1H), 2.53 – 2.41 (m, 4H), 2.23 (ddd, J = 15.7, 7.1, 2.6, 4H), 1.96 (t, J = 7.3, 1H), 1.88 – 1.76 (m, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 172.1, 171.6, 156.8, 136.6, 129.7, 129.2, 128.3, 126.1, 123.4, 117.0, 101.6, 99.8, 83.0, 82.9, 78.2, 72.0, 71.6, 69.3, 69.2, 68.5, 66.6, 32.7, 32.6, 23.6, 23.5, 17.7, 17.6. HRMS Calcd for C₃₁H₃₂O₈Na [M + Na]⁺ 555.1995, found 555.1992.
Compound 15B (56 mg, 63%); white solid; mp 128.0-129.0°C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.45 (dd, $J = 6.5, 2.9, 2$H), 7.40 – 7.28 (m, 5H), 7.08 (dd, $J = 14.9, 7.6, 3$H), 5.53 (s, 1H), 5.33 (t, $J = 9.4, 1$H), 5.10 (d, $J = 7.6, 1$H), 4.39 (dd, $J = 10.5, 4.8, 1$H), 3.94 – 3.72 (m, 3H), 3.65 (td, $J = 9.6, 4.9, 1$H), 2.65 – 2.52 (m, 2H), 2.26 (td, $J = 6.9, 2.6, 1$H), 2.02 – 1.79 (m, 3H).  
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 173.1, 156.8, 136.8, 129.7, 129.1, 128.3, 126.1, 123.4, 117.0, 101.6, 101.6, 83.2, 78.2, 73.5, 73.3, 69.2, 68.6, 66.6, 32.9, 23.7, 17.6.

For compound 16: 6-heptynoic acid (0.16 mL, 1.2 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.1 mL, 1.2 mmol) was added to mixture slowly and followed by 1 drop anhydrous DMF. The mixture was stirred at room temperature for 2 hours at which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of ester synthesis.

Compound 16A (43 mg, 30%); white solid; mp 92.0-93.0°C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.44 (dd, $J = 6.7, 2.7, 2$H), 7.40 – 7.28 (m, 5H), 7.08 (t, $J = 7.4, 1$H), 7.02 – 6.96 (m, 2H), 5.54 (s, 1H), 5.43 (t, $J = 9.4, 1$H), 5.31 (t, $J = 8.5, 1$H), 5.20 (d, $J = 7.7, 1$H), 4.42 (dd, $J = 10.5, 4.9, 1$H), 3.83 (dd, $J = 22.0, 9.9, 2$H), 3.68 (td, $J = 9.7, 4.9, 1$H), 2.43 – 2.27 (m, 4H), 2.14 (dd, $J = 9.6, 7.0, 2.6, 4$H), 1.96 – 1.88 (m, 2H), 1.79 – 1.64 (m, 4H), 1.51 (dq, $J = 14.2, 7.2, 4$H).  
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 172.5, 171.9, 156.8, 136.7, 129.7, 129.2, 128.3, 126.1, 123.4, 116.8, 101.6, 99.7, 83.8, 83.7, 78.2, 71.9, 71.5, 68.7, 68.6, 68.5, 66.6, 33.6, 33.5, 27.6, 27.5, 23.9, 23.8, 18.1, 18.0. HRMS Calcd for C$_{33}$H$_{37}$O$_8$ [M + H]$^+$ 561.2488, found 561.2491.
Compound **16B** (49 mg, 42%); white solid; mp 127.0-129.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45 (dd, $J = 6.5$, 3.0, 2H), 7.41 – 7.29 (m, 5H), 7.08 (dd, $J = 15.1$, 7.6, 3H), 5.52 (s, 1H), 5.33 (t, $J = 9.4$, 1H), 5.10 (d, $J = 7.6$, 1H), 4.37 (dt, $J = 27.3$, 13.7, 1H), 3.94 – 3.70 (m, 3H), 3.65 (td, $J = 9.6$, 4.9, 1H), 2.44 (t, $J = 7.3$, 2H), 2.14 (td, $J = 7.0$, 2.6, 2H), 1.93 (t, $J = 2.6$, 1H), 1.78 (tt, $J = 13.3$, 6.6, 2H), 1.65 – 1.47 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.5, 156.8, 136.8, 129.7, 129.2, 128.3, 126.1, 123.4, 117.0, 101.6, 101.6, 84.0, 78.2, 73.4, 73.2, 68.6, 68.5, 66.6, 33.7, 27.4, 24.0, 18.0. HRMS Calcd for C$_{26}$H$_{29}$O$_7$ [M + H]$^+$ 453.1913, found 453.1913. HRMS Calcd for C$_{25}$H$_{27}$O$_7$ [M + H]$^+$ 439.1757, found 439.1761.

For compound **17**: 10,12-tricosadiynoic acid (282 mg, 0.8 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.09 mL, 1.0 mmol) was added to mixture slowly and followed by 1 drop anhydrous DMF. The mixture was stirred at room temperature for 2 hours at which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of ester synthesis.

Compound **17A** (11 mg, 5%); white solid; mp 41.0-43.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.44 (dd, $J = 6.6$, 3.0, 3H), 7.39 – 7.34 (m, 3H), 7.33 – 7.27 (m, 1H), 7.08 (t, $J = 7.4$, 1H), 6.99 (d, $J = 7.8$, 2H), 5.51 (s, 1H), 5.43 (t, $J = 9.4$, 1H), 5.33 – 5.27 (m, 1H), 5.20 (d, $J = 7.7$, 1H), 4.50 – 4.33 (m, 1H), 3.93 – 3.76 (m, 2H), 3.67 (tt, $J = 13.0$, 6.4, 1H), 2.50 – 2.10 (m, 8H), 1.81 – 0.51 (m, 64H), 0.88 (t, $J = 6.8$, 10H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 172.8, 172.2, 156.8, 136.7, 129.6, 129.1, 128.2, 126.1, 123.3, 116.8, 101.5, 99.7, 78.3, 77.6, 77.4, 71.7, 71.4, 68.6, 66.6,
Compound **17B** (90 mg, 63%); white solid; mp 49.0-51.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45 (dd, $J = 6.3$, 3.0, 2H), 7.34 (ddd, $J = 16.1$, 6.9, 2.2, 6H), 7.12 – 7.03 (m, 2H), 5.53 (s, 1H), 5.31 (t, $J = 9.4$, 1H), 5.11 (d, $J = 7.6$, 1H), 4.38 (dt, $J = 12.1$, 6.1, 1H), 3.81 (ddd, $J = 29.2$, 17.9, 8.7, 3H), 3.65 (td, $J = 9.6$, 4.7, 1H), 2.46 – 2.37 (m, 2H), 2.23 (dd, $J = 16.1$, 7.5, 7H), 1.73 – 1.01 (m, 25H), 0.88 (t, $J = 6.8$, 7H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.0, 156.8, 136.8, 129.7, 129.1, 128.2, 126.1, 123.4, 117.0, 101.7, 101.5, 78.2, 77.6, 77.5, 73.5, 73.3, 68.6, 66.7, 65.3, 65.2, 34.3, 31.9, 29.8, 29.7, 29.6, 29.5, 29.3, 29.1, 29.0, 28.9, 28.8, 28.7, 28.4, 28.3, 25.0, 24.7, 22.7, 19.2, 19.1, 14.1. HRMS Calcd for C$_{44}$H$_{61}$O$_7$ [M + H]$^+$ 701.4417, found 701.4423.

For compound **18**: 10,12-pentacosadiynoic acid (260 mg, 0.7 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.09 mL, 1.0 mmol) was added to mixture slowly and followed by 1 drop anhydrous DMF. The mixture was stirred at room temperature for 2 hours at which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of ester synthesis.

Compound **18A** (9 mg, 4%); white solid; mp 56.0-58.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 – 7.40 (m, 2H), 7.39 – 7.27 (m, 5H), 7.08 (t, $J = 7.4$, 1H), 6.99 (d, $J = 8.4$, 2H), 5.53 (s, 1H), 5.43 (t, $J = 9.4$, 1H), 5.34 – 5.27 (m, 1H), 5.20 (d, $J = 7.7$, 1H), 4.40 (dt, $J = 13.9$, 7.0, 1H), 2.59 (s, 1H), 2.12 (s, 3H). HRMS Calcd for C$_{69}$H$_{100}$O$_8$Na [M + Na]$^+$ 1079.7316, found 1079.7306.
3.90 – 3.76 (m, 2H), 3.67 (ddd, J = 18.3, 11.6, 6.7, 1H), 2.37 – 2.16 (m, 14H), 1.70 – 1.11 (m, 54H), 0.88 (t, J = 6.8, 8H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 172.8, 172.2, 156.8, 136.7, 129.6, 129.1, 128.2, 126.1, 123.3, 116.8, 101.5, 99.7, 78.3, 77.6, 77.4, 71.7, 71.3, 68.5, 66.6, 65.3, 65.2, 34.2, 34.1, 31.9, 29.6, 29.5, 29.3, 29.1, 29.0, 28.9, 28.8, 28.7, 28.4, 28.3, 25.0, 24.9, 22.7, 19.2, 19.1, 14.1. HRMS Calcd for C$_{65}$H$_{92}$O$_8$ [M + H]$^+$ 1001.6870, found 1001.6871.

Compound 18B (89 mg, 65%); white solid; mp 39.0-40.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.44 (dd, J = 6.5, 2.9, 2H), 7.39 – 7.28 (m, 5H), 7.08 (dd, J = 12.1, 7.6, 3H), 5.53 (s, 1H), 5.31 (t, J = 9.4, 1H), 5.11 (d, J = 7.6, 1H), 4.39 (dd, J = 10.5, 4.8, 1H), 3.91 – 3.71 (m, 3H), 3.65 (td, J = 9.7, 4.9, 1H), 2.47 – 2.14 (m, 5H), 1.79 – 1.00 (m, 27H), 0.88 (t, J = 6.8, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 174.0, 156.8, 136.8, 129.7, 129.2, 128.2, 126.1, 123.4, 117.0, 101.7, 101.5, 78.2, 77.6, 73.5, 73.4, 68.6, 66.7, 65.3, 65.2, 34.3, 31.9, 29.6, 29.5, 29.3, 29.1, 29.0, 28.9, 28.8, 28.7, 28.4, 28.3, 25.0, 24.7, 22.7, 19.2, 14.1. HRMS Calcd for C$_{42}$H$_{57}$O$_7$ [M + H]$^+$ 673.4104, found 673.4105.
References


Chapter III

Synthesis and Characterization of Unprotected D-Glucosamine Based Low Molecular Weight Gelators.

Abstract: Glucosamine is an amino sugar present in animal bones, bone marrow, cell walls of fungi and many higher organisms. The amino group of 2-glucosamine allows the molecule to be functionalized with different functional groups. Our group has utilized the 4,6-benzylidene acetate protected D-glucosamine 1 as a template and synthesized various amide, urea and carbamate derivatives. Many of the derivatives were found to be efficient gelators for aqueous DMSO and aqueous ethanol solutions, and only a few of them can form gel in water. For biological applications, hydrogelators are more advantageous than organogelators. In this chapter, there are two main goals. The first goal is to find out the importance of the benzylidene acetal group by using compound 2 as the template for the synthesis of potential gelators; the second main goal is to synthesize and evaluate whether the unprotected D-glucosamine 3 derivatives can serve as efficient low molecular weight hygrogelators.

Keyword: hydrogelator, glucosamine.
**Introduction**

Glucosamine and N-acetyl glucosamine are naturally present in many organisms. Chitosan is partially made by glucosamine. Chitin is a polymer of N-acetyl glucosamine. The structure of chitin is shown in compound 4.¹ Glucosamine is widely used as a dietary supplement for supporting function and structure of joints. It is also used to relieve osteoarthritis. The medicinal effect of glucosamine may be anti-inflammatory.

![Structure of Chitin (compounds 4)](image)

The glucosamine derivatives have been studied in different research areas.²⁻²⁰ Glucosamines were attached to carboxylic acids which were associated with nanotubes.²¹ The resulting nanotubes can dissolve in water from 0.1 mg/mL to 0.3 mg/mL. South Korean researchers synthesized copper-glucosamine microcubes to study biofunctionalized microstructure electrodes.²²

In gelator area, derivatives of glucosamine have been studied along with other sugars. Due to the natural abundance, the polymer form of glucosamine chitin was one of the first materials to be tested. Chitin is a very good gelator which can form gel under mild condition.¹ For glucosamine based low molecular weight gelators, Pavel Drasar research group studies amides
formed by steroid and bile acids with D-glucosamine. The gelation tests showed negative results. Bin Xu research group linked D-glucosamine with L/D-phenylalanine and naphthyl group. The resulting two compounds can form gel in water at 2 mg/mL. The structures of two compounds are shown below.

![Chemical structures](image)

**Figure 3.1 Structures of glucosamine based hydrogelators**

Bing Xu, etc also examined the biocompatibility of the two gels. In cytotoxicity assay, compound 5 showed 73.8% Hela cell survival in 100 µM in 24 hours. The compound 6 showed 79.0% at the same condition. Based on the above results, compound 6 was used in wound healing test on mouse model. In the comparison with controlled group, mice treated with gel showed much faster healing and smaller scar.

Our group has been studying derivatives of D-glucosamine including carbamates, amides, and ureas as low molecular weight gelators. Using the 4, 6-benzylidene acetal protected headgroup 1 as the starting material, ureas 7 and amides 8 have been synthesized and evaluated. The glucosamine head group reacted with acyl chloride, isocyanate, chloroformate to form...
amides, ureas, carbamates. The R group included straight chain alkyl, terminal alkyne, aromatic rings.  

![Images of structures 1, 7, and 8]

Figure 3.2 The common structures of urea and amide

All the products of amide and urea can form gels in DMSO: H₂O (1:2), EtOH: H₂O (1:2). The hexyl urea, heptyl urea and heptyl amide formed gel at 1 mg/mL in DMSO water mixture. Phenyl amide gelled water at 2 mg/mL. When we compare these results with results of esters from the first chapter, we can conclude that amides and ureas are much better. The glucosamine derivatives contain extra hydrogen bonding groups, the NH groups.

In the previous chapter, we systemically studied the effect of different group at anomeric position. Now we switch our attention to the 4, 6 position. Benzylidene was widely used as the protecting group as we can see from Chapter 1 and compound 1. The phenyl ring provides the π-π stacking in gelation process. Other functional groups at the 4, 6 position were not fully studied, so we want to study the structure and gelation relationship by changing the protecting group to isopropylidene and no protecting group.
Another reason for this research is when it comes to biological applications, low molecular weight hydrogelators are more favored. To synthesize more hydrogelators, we hypothesized that by removing the 4, 6-protective groups after introducing functional groups at 2, 3-positions, and the polarity changes significantly.

To synthesize these, we can deprotect the benzylidene acetal directly; however, the byproduct benzaldehyde was not easily removed. Phase-phase extraction was used and benzaldehyde was in organic phase. However to obtain the product we have to remove water and in some situation compounds with aromatic functional group can also dissolve in organic phase. To simplify workup, we decided to replace benzyl with isopropyl. Then the byproduct was acetone and in this case no workup or purification was needed.
**Results and Discussion**

Head group 2 was synthesized in three steps from N-acetyl D-glucosamine 9. Treatment of 6 with methanol in the presence of acidic ion exchange resin gave the methyl glycoside 10 in 91% yield. Protection of the 4- and 6- hydroxyl groups of 7 with 2, 2-dimethoxy propane afforded the acetal-protected analog 11 in 90% yield. Head group 2 was then obtained by deprotecting the 2-amino group under basic conditions, which took place in 85% yield.

![Scheme 3.1 The synthesis of 4, 6-O-isopropylidene-methyl-D-glucosamine.](image)

With head group 2 in hand, amides derivatives with the general structure 12 were synthesized by reacting head group 2 with various acyl chlorides in the presence of pyridine. Ureas with the general structure 14 were made by reacting head group 2 with various
isocyanates. The selection of acyl chlorides and isocyanates were based on the availability of starting materials and our previous studies of ureas and amides with the general structures 7 and 8. For the amides, we synthesized the 5 and 10 carbon chain terminal alkynoyl, 6, 10, and 22 carbon chain saturated alkanoyl, benzoyl and naphthoyl derivatives. Yields ranged from 76-95%. The acyl chloride of 17, 18, 22 were synthesized in situ. For the ureas, the undecynyl, octanoyl, dodecanyl, phenyl, naphthyl, and cyclohexyl derivatives were synthesized, in 65-92% yield. The isocyanate of 27, 28 were synthesized through Curtius rearrangement. The amides and ureas yields and gel tests results are shown in Table 3.1, 3.2, 3.3, 3.4.

![Structures of compounds 16-22](image.png)

Table 3.1 Yields of amides

<table>
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<tr>
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<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
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<td>85 %</td>
<td>83 %</td>
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Table 3.2 Library of amide derivatives of 12 and their corresponding minimum gelation concentrations (MGCs) in mg/mL.

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<td>S</td>
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All concentrations are in mg/mL; G, gel at room temperature; the numbers after G are minimum gelation concentrations; P, precipitation; S, soluble at~20 mg/mL; the ratios of solvents are in parenthesis.
Table 3.3 Yields of Ureas

<table>
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<td>76 %</td>
<td>75 %</td>
<td>95 %</td>
<td>69 %</td>
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Table 3.4 Library of urea derivatives of 9 and their corresponding minimum gelation concentrations (MGCs) in mg/mL.

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<th>EtOH</th>
<th>EtOH:H₂O (1:2)</th>
<th>DMSO:H₂O (1:2)</th>
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</thead>
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<td>I</td>
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<td>S</td>
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All concentrations are in mg/mL; G, gel at room temperature; the numbers after G are minimum gelation concentrations; P, precipitation; S, soluble at~20 mg/mL; the ratio of solvents in parenthesis.

Unfortunately, none of the amides were able to form gels in any of the 5 solvents. This is not completely unexpected; we knew that replacing the benzylidene acetal group with an isopropylidene acetal would eliminate the possibility for intermolecular π-π stacking interactions among the molecules, which can help contribute to gel formation. Among the ureas, two of the compounds, the benzyl and naphthyl derivatives, were able to form gels in aqueous DMSO at concentrations of 20 mg/mL. It seems that the phenyl and naphthyl rings provide an alternative
π-π stacking group, which is essential for gelation. However, the gelation efficiency is not as good as the phenyl and naphthyl ureas of 4, 6-O-benzylidene-methyl-α-D-glucosamine with the general structure 7.

The amides and ureas were treated with 85% acetic acid and stirred at room temperature for around 6 hours to remove the isopropylidene acetal functionality. After the reaction was done, the excess acetic acid and acetone byproduct were removed by evaporation under a stream of nitrogen, without need for further purification. The deprotected products (13, 15) were then screened for gelation in water, hexane, ethanol, and aqueous mixtures of ethanol and DMSO; the yields and gel tests results are shown in Table 3.5, 3.6, 3.7, 3.8.
Table 3.5 Yields of deprotected amides

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Table 3.6 Library of amide derivatives of 23 and their corresponding minimum gelation concentrations (MGCs) in mg/mL.

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<th>EtOH:H$_2$O(1:2)</th>
<th>DMSO:H$_2$O(1:2)</th>
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<td>I</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<tr>
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<td>G 9</td>
<td>G 8</td>
<td>G 5</td>
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<td>S</td>
<td>G 20</td>
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</table>

All concentrations are in mg/mL; G, gel at room temperature; the numbers after G are minimum gelation concentrations; P, precipitation; S, soluble at ~20 mg/mL; the ratio of solvents in parenthesis.
Table 3.7 Yields of deprotected ureas

<table>
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<th>Compound</th>
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<td>Yield</td>
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<td>95 %</td>
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Table 3.8 Library of urea derivatives of 24 and their corresponding minimum gelation concentrations (MGCs) in mg/mL.

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<th>EtOH:H₂O (1:2)</th>
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<td>41</td>
<td>I</td>
<td>I</td>
<td>G 10</td>
<td>G 7</td>
<td>P</td>
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</tbody>
</table>
All concentrations are in mg/mL; G, gel at room temperature; the numbers after G are minimum gelation concentrations; P, precipitation; S, soluble at ~20 mg/mL; the ratios of solvents are in parenthesis.

Figure 3.3a shows the hydrogel of 40 at 2.5 mg/mL. The picture shows some liquid comes from the top. So the minimum concentration is greater than 2.5 mg/mL, at 3 mg/mL the gel was stable. Therefore the safe estimate of the MIC is 3 mg/mL.

![Figure 3.3a](image)

Figure 3.3 a) A photograph of a gel formed by compound 40 in water at 2.5 mg/mL. b) A photograph of a gel formed by compound 41 in DMSO: H2O (1:2) at 7 mg/mL.

For amide derivatives, after the removal of isopropyl group at 4, 6-position, gelation properties improved significantly. Three compounds formed gel in different solvents. The 22 carbon chain amide 39 was the best one. It can gel 9 mg/mL in ethanol, 8 mg/mL in 33% aqueous solution of DMSO and 5 mg/mL in 33% aqueous solution of ethanol. The 10 carbons terminal acetylene amide 40 can gel in 33% aqueous solution of DMSO or ethanol. It also gelled water at 20 mg/mL. The phenyl amide only forms gel in ethanol at 10 mg/mL. Naphthal amide does not form any gel. Compare with the amides before deprotection, the molecules have two more hydroxy groups which make them more polar and hydrophilic. The main driving force after
deprotection is the balance between hydrophobic and hydrophilic interaction not the π-π stacking. The deprotected amides behaving well all have very long carbon chains which make the molecules hydrophobic. At the same time 33% aqueous DMSO or ethanol gives the right amount of water.

For urea derivatives, four compounds form gel in different solvents. Compare with the urea derivatives before deprotection, which only two compounds gel in one solvents, the gelation property improve dramatically. Naphthal urea 38 and 10 carbon terminal acetylene urea 40 gel in water, 33% aqueous DMSO or ethanol. They gel water at 4mg/mL and 3 mg/mL, which are very good hydrogelators. 22 carbons urea 41 gels ethanol at 10mg/mL and 33% aqueous DMSO at 7 mg/mL. The improved gelation property is mainly due to the balance of hydrophobic and hydrophilic interaction. Four compounds all have long carbon chain or aromatic ring system, after the introduction of two new hydroxyl groups, the molecules are balanced.

Comparing deprotected ureas and deprotected amides, the deprotected ureas performed better than deprotected amides. This result is consistent with our previous results using different head groups. The urea derivatives have more hydrogen bond donor than amide derivatives.

Some of images from optical microscope are shown in Figures 3.4-3.6. The gel formed by compound 30 consisted of thin fibers, as shown in Figure 3.3. The very bright area indicated that lots of fibers packed there. The morphology of compound 35 was quite different from others. It
seemed that fibers all connected with each other and formed a big piece of sheet. The gel pictures of compound 37 were taken at 3 mg/mL and we can see the small tubes instead of long fibers.

Figure 3.4 500x Optical micrographs of gel formed by compound 30 at 10 mg/mL in EtOH: H$_2$O (1:2).

Figure 3.5 500x Optical micrographs of gel formed by compound 35 at 20 mg/mL in DMSO:H$_2$O (1:2).
Figure 3.6 Optical micrographs of a gel formed by compound 37 at 3 mg/mL in water, the left was at 200x magnification, and the right was 500x magnification.
Conclusions

Amide and urea series of 4, 6-O-isopropylidene-Methyl-α-D-glucosamine has been synthesized through straight reactions with high yields. The gelation property has been tested in 5 different solvent. Compare the results of amides and ureas using 4, 6-O-benzylidene-methyl-α-D-glucosamine head group, we found that the π-π stacking from phenyl ring can significantly affect the gelation. Amide and urea series of methyl-α-D-glucosamine were synthesized after acid removal of isopropyl group. The gelation property changed dramatically especially for ureas. Naphthyl urea 38 and other three long alkyl chain ureas 39, 40, 41 formed gel in DMSO:H₂O (1:2), EtOH:H₂O (1:2), water. Urea 40 gelled water at 3 mg/mL. These compounds shared some common features like long straight carbon chain which can contribute to the balance between hydrophobicity and hydrophilicity.
Experimental section

General procedure for the synthesis of amide

4,6-O-Isopropylidene-Methyl-α-D-Glucosamine (50 mg, 0.214 mmol) was dissolved in anhydrous THF with pyridine (1.07 mmol). The corresponding acyl chloride (0.214 mmol) was added to the solution, which was then stirred at room temperature for 8 hours. The reaction mixture was worked up by DCM extraction. The crude product can be purified by flash chromatography on silica gel using the solvent system hexane and ethyl acetate.

Compound 16 (109 mg, 96%); white solid; mp 107.0-108.5 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.92 (d, \(J = 8.6\), 1H), 4.66 (d, \(J = 3.8\), 1H), 4.13 (td, \(J = 9.3\), 3.8, 1H), 3.84 (dd, \(J = 10.6\), 4.5, 1H), 3.79 – 3.65 (m, 2H), 3.65 – 3.52 (m, 2H), 3.34 (s, 3H), 2.21 (t, \(J = 7.3\), 2H), 1.61 (quintet, \(J = 7.3\), 2H), 1.50 (s, 3H), 1.41 (s, 3H), 1.38 – 1.21 (m, 5H), 0.87 (t, \(J = 6.8\), 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 174.9, 100.0, 99.0, 77.6, 77.2, 76.9, 74.9, 71.2, 63.4, 62.4, 55.3, 54.3, 36.7, 31.5, 29.3, 25.4, 22.5, 19.2, 14.1.

For compound 17: 5-hexynoic acid (46 mg, 0.4 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.07 mL, 0.8 mmol) was added to mixture slowly and the mixture was stirred at room temperature for 2 hours at which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of amide synthesis.
**Compound 17** (86 mg, 76%); white solid; Compound is extremely hygroscopic, and absorbs moisture to become gummy oil within a few minutes. Thus, melting point could not be obtained. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.98 (d, $J = 8.7$, 1H), 4.66 (d, $J = 3.8$, 1H), 4.15 (td, $J = 9.4$, 3.8, 1H), 3.84 (dd, $J = 10.6$, 4.5, 1H), 3.80 – 3.66 (m, 2H), 3.66 – 3.53 (m, 2H), 3.38 (s, 3H), 2.38 (t, $J = 7.3$, 2H), 2.29-2.23 (m, 2H), 1.98 (t, $J = 2.6$, 1H), 1.92 – 1.80 (m, 2H), 1.51 (s, 3H), 1.42 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.8, 100.0, 99.0, 83.6, 74.9, 71.1, 69.5, 63.5, 62.4, 55.9, 55.4, 54.3, 35.1, 29.3, 24.1, 19.3, 17.8.

For compound 18:10-undecynoic acid (66 mg, 0.4 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.07 mL, 0.8 mmol) was added to mixture slowly and the mixture was stirred at room temperature for 2 hours at which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of amide synthesis.

**Compound 18** (144 mg, 75%); white solid; mp 97.0-98.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.88 (d, $J = 8.5$, 1H), 4.66 (d, $J = 3.8$, 1H), 4.15 (td, $J = 9.3$, 3.8, 1H), 3.85 (dd, $J = 10.7$, 4.3, 1H), 3.80 – 3.65 (m, 2H), 3.65 – 3.52 (m, 2H), 3.35 (s, 3H), 3.20 (s, 1H), 2.22 (t, $J = 7.5$, 2H), 1.61 (dd, $J = 13.9$, 6.9, 2H), 1.52 (s, 3H), 1.42 (s, 3H), 1.24 (s, 36H), 0.86 (t, $J = 6.7$, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.0, 100.0, 99.0, 74.9, 71.4, 63.4, 62.4, 55.3, 54.3, 36.8, 32.1, 29.9, 29.8, 29.7, 29.5, 29.4, 29.3, 25.8, 22.9, 19.3, 14.3.
Compound 19 (119 mg, 95%); white solid; mp 74.5-76 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.77 (d, $J = 7.3$, 2H), 7.48 (t, $J = 7.4$, 1H), 7.40 (t, $J = 7.5$, 2H), 6.59 (d, $J = 8.6$, 1H), 4.79 (d, $J = 3.8$, 1H), 4.37 (td, $J = 9.3$, 3.8, 1H), 3.94 – 3.73 (m, 3H), 3.70 – 3.59 (m, 2H), 3.38 (s, 3H), 1.52 (s, 3H), 1.43 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.7, 133.9, 132.0, 128.7, 127.4, 100.1, 99.1, 74.9, 71.1, 63.5, 62.4, 55.4, 54.8, 29.3, 19.3.

Compound 20 (92 mg, 69%); white solid; mp 198.0-199.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.26 – 8.16 (m, 1H), 7.82 – 7.71 (m, 2H), 7.52 (dd, $J = 7.0$, 1.0, 1H), 7.45 – 7.38 (m, 2H), 7.32 – 7.27 (m, 1H), 6.36 (d, $J = 8.8$, 1H), 4.77 (d, $J = 8.1$, 1H), 4.37 (td, $J = 9.6$, 4.0, 1H), 3.82 – 3.65 (m, 3H), 3.63 – 3.47 (m, 2H), 3.33 – 3.22 (m, 4H), 1.42 (s, 3H), 1.35 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.7, 134.0, 133.7, 130.9, 130.2, 128.4, 127.4, 126.6, 125.5, 125.4, 124.8, 100.0, 99.1, 74.9, 71.0, 63.6, 62.4, 55.4, 54.7, 29.2, 19.2.

Compound 21 (92 mg, 85%); white solid; mp 86.0-88.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.81 (t, $J = 20.7$, 1H), 4.66 (d, $J = 3.8$, 1H), 4.17 (td, $J = 9.3$, 3.8, 1H), 3.89 – 3.68 (m, 3H), 3.65– 3.56(m, 2H), 3.37 (s, 3H), 3.08 (d, $J = 3.1$, 1H), 2.24 (t, $J=7.6$, 2H), 1.53 (s, 3H), 1.44 (s, 3H), 1.37–1.19 (m, 9H), 0.87 (t, $J = 6.7$, 3H ). $^{13}$C NMR (101 MHz, CDCl$_3$): δ 174.8, 99.8, 98.8, 74.7, 71.4, 63.2, 62.2, 55.1, 54.1, 36.7, 31.6, 29.1, 29.0, 25.6, 22.6, 19.1, 14.0.

For compound 22: docosanoic acid (140 mg, 0.4 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.04 mL, 0.5 mmol) was added to mixture slowly and followed by 1 drop anhydrous DMF. The mixture was stirred at room temperature for 2 hours at
which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of amide synthesis.

Compound 22 (99 mg, 83%); white solid; mp 53.0-54.0 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.83 (t, \(J = 19.0, 1H\)), 4.66 (d, \(J = 3.9, 1H\)), 4.19 – 4.12 (m, 1H), 3.88–3.68 (m, 3H), 3.64–3.57 (m, 2H), 3.36 (s, 3H), 2.3–2.12 (m, 4H), 1.95–1.91 (m, 1H), 1.84–1.76 (m, 1H), 1.68–1.57(m, 2H), 1.52 (s, 3H), 1.43(s, 3H), 1.41–1.21 (m, 9H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 174.7, 99.8, 98.8, 74.7, 71.3, 68.1, 63.2, 62.2, 55.1, 54.0, 36.6, 29.1, 29.1, 29.0, 28.9, 28.6, 28.4, 25.5, 19.0, 18.3.

**General procedure for the synthesis of ureas.**

4,6-O-Isopropylidene-Methyl-\(\alpha\)-D-Glucosamine (50 mg, 0.214 mmol) was dissolved in anhydrous THF. The corresponding isocyanate (0.214 mmol) was added to the solution, which was then stirred at room temperature for 6 hours. The solvent was removed under N\(_2\). The crude product can be purified by flash chromatography on silica gel using the solvent system 2% methanol in DCM.

Compound 23 (140 mg, 92%); white solid; mp 105.0-107.0 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.52 (s, 1H), 7.29 – 7.17 (m, 3H), 6.98 (m, 1H), 5.58 (t, \(J = 19.0, 1H\)), 4.72 (d, \(J = 3.8, 1H\)), 4.04–3.95 (m, 1H) 3.88–3.73 (m, 3H), 3.67 – 3.58 (m, 2H), 3.34 (s, 3H), 1.50 (s, 3H), 1.41
(s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$): δ 156.6, 138.6, 129.0, 123.2, 120.1, 99.9, 99.4, 74.6, 71.1, 63.3, 62.3, 55.2, 55.1, 19.1.

Compound 24 (71 mg, 92%); white solid; mp 110.0-111.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.08 (dd, $J = 18.8$, 8.1, 2H), 4.67 (d, $J = 3.8$, 1H), 4.03 (s, 1H), 3.96 – 3.43 (m, 5H), 3.36 (s, 3H), 2.16 (s, 1H), 1.90 (d, $J = 10.8$, 2H), 1.67 (dd, $J = 9.4$, 3.9, 2H), 1.52 (s, 3H), 1.42 (s, 3H), 1.37–1.25 (m, 3H), 1.18–1.05 (m, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$): δ 158.4, 99.8, 99.4, 74.7, 71.7, 63.2, 62.3, 55.3, 55.1, 49.2, 33.7, 33.5, 29.0, 25.5, 24.8, 19.1.

Compound 25 (74 mg, 85%); white solid; mp 132.0-133.0 °C. $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.30 – 7.95 (m, 1H), 7.95 – 7.78 (m, 1H), 7.70 (d, $J = 8.2$, 1H), 7.60 (d, $J = 7.3$, 1H), 7.57 – 7.39 (m, 3H), 5.37 (d, $J = 8.7$, 1H), 4.62 (d, $J = 3.8$, 1H), 4.17 – 3.94 (m, 1H), 3.83 – 3.48 (m, 6H), 3.15 (s, 3H), 1.49 (s, 3H), 1.39 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$): δ 157.7, 134.4, 133.0, 128.5, 126.5, 126.3, 126.3, 125.8, 122.3, 121.9, 99.8, 99.2, 74.6, 71.5, 63.2, 62.2, 55.3, 55.1, 29.0, 19.0.

Compound 26 (73 mg, 91%); white solid; mp 53.0-54.0 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ 5.25 – 5.15 (m, 2H), 4.66 (d, $J = 3.8$, 1H), 3.89 – 3.68 (m, 4H), 3.63 – 3.56 (m, 2H), 3.35 (s, 3H), 3.20 – 3.02 (m, 2H), 1.52 (s, 3H), 1.50 – 1.43 (m, 2H), 1.42 (s, 3H), 1.36 – 1.17 (m, 8H), 0.86 (t, $J = 6.8$, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$): δ 159.2, 99.8, 99.4, 74.7, 71.5, 63.2, 62.3, 55.2, 55.1, 40.6, 31.7, 29.0, 29.0, 26.9, 22.5, 19.1, 14.0.
For compound 27: 10-undecynoic acid (39 mg, 0.2 mmol) was mixed with triethylamine (0.06 mL, 0.4 mmol) and diphenylphosphoryl azide (0.046 mL, 0.4 mmol) in 2 mL anhydrous THF. The mixture was heated at 60 °C for 2 hours and the reaction was complete. The product was used directly following the general procedure of urea synthesis.

Compound 27 (55 mg, 62%); white solid; mp 41.0-42.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.00 – 4.78 (m, 2H), 4.65 (dd, $J = 13.3, 9.6, 1$H), 3.89–3.57 (m, 6H), 3.36 (s, 3H), 3.13 (d, $J = 6.5, 2$H), 2.29 – 2.13 (m, 2H), 1.93 (t, $J = 2.6, 1$H), 1.81 (s, 1H), 1.53 (s, 3H), 1.51-1.45 (m, 3H), 1.43 (s, 3H), 1.34-1.29 (m, 8H). $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 159.0, 99.8, 99.3, 74.7, 71.9, 68.1, 63.1, 62.3, 55.3, 55.1, 40.7, 30.0, 29.1, 29.1, 29.0, 28.6, 28.4, 26.8, 19.1, 18.3.

For compound 28: docosanoic acid (146 mg, 0.4 mmol) was mixed with triethylamine (0.12 mL, 0.8 mmol) and diphenylphosphoryl azide (0.18 mL, 0.8 mmol) in 2 mL anhydrous THF. The mixture was heated at 60 °C for 2 hours and the reaction was complete. The product was used directly following the general procedure of urea synthesis.

Compound 28 (108 mg, 65%); white solid; mp 92.0°C-94.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.07 – 4.91 (m, 2H), 4.66 (t, $J = 6.8, 1$H), 3.91 – 3.68 (m, 4H), 3.65 – 3.56 (m, 2H), 3.36 (s, 3H), 3.21 – 3.06 (m, 2H), 1.53 (s, 3H), 1.50-1.44 (m, 1H), 1.43 (s, 3H), 1.37 – 1.16 (m, 37H), 0.87 (t, $J = 6.8, 3$H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 159.0, 99.8, 99.3, 74.7, 71.8, 63.2, 62.3, 55.3, 55.1, 40.7, 31.9, 30.1, 29.7, 29.6, 29.6, 29.3, 29.3, 29.1, 26.9, 22.7, 19.1, 14.1.
General procedure for deprotected ureas and amides.

Typically, the urea or amide product (50mg) from the previous step was mixed with 2ml 85% acetic acid and stirred at room temperature for 6 hours. The reaction mixture was put under nitrogen and then under vacuum. The leftover solid was pure and no further purification was needed.

Compound 29 (42 mg, 96%); white solid; mp 157.0-158.0 °C. $^1$H NMR (400 MHz, DMSO) $\delta$ 7.60 (d, $J$ = 8.0, 1H), 4.94 (d, $J$ = 5.4, 1H), 4.64 (d, $J$ = 5.5, 1H), 4.49 (dd, $J$ = 12.2, 4.8, 1H), 3.73 – 3.55 (m, 2H), 3.51 – 3.35 (m, 2H), 3.21 (s, 3H), 3.17 – 3.02 (m, 2H), 2.15 – 1.99 (m, 2H), 1.54 – 1.37 (m, 2H), 1.33 – 1.11 (m, 3H), 0.83 (t, $J$ = 6.9, 4H).$^{13}$C NMR (101 MHz, DMSO): $\delta$ 172.5, 97.9, 72.7, 70.9, 70.7, 60.8, 54.3, 53.7, 35.1, 30.8, 25.0, 21.9, 13.9. HRMS Calcd for C$_{13}$H$_{26}$NO$_6$[M + 1]$^+$, 298.1760; found, 298.1756.

Compound 30 (42 mg, 96%); white solid; mp 155.0-156.0 °C. $^1$H NMR (400 MHz, DMSO) $\delta$ 7.69 (d, $J$ = 8.1, 1H), 4.51 (d, $J$ = 3.5, 1H), 3.72 – 3.54 (m, 2H), 3.50 – 3.36 (m, 2H), 3.22 (s, 3H), 3.08 (dd, $J$ = 21.4, 12.3, 2H), 2.75 (t, $J$ = 2.6, 1H), 2.26 – 2.05 (m, 4H), 1.64 (p, $J$ = 7.3, 2H).$^{13}$C NMR (101 MHz, DMSO): $\delta$ 171.8, 97.9, 84.3, 72.7, 71.4, 70.8, 70.7, 60.8, 54.3, 53.7, 34.1, 24.4, 17.4. HRMS Calcd for C$_{13}$H$_{21}$NO$_6$Na$^+$[M + Na]$^+$, 310.1267; found, 310.1265.

Compound 31 (42 mg, 90%) white solid; mp 149-151°C. NMR spectrum only showed the peaks between 1ppm and 2 ppm. HRMS calculated for C$_{29}$H$_{58}$NO$_6$ [M+H], 516.4264; found, 516.4272.
Compound 32 (43 mg, 97%); white solid; mp 220.0-221.0°C. $^1$H NMR (400 MHz, DMSO) $\delta$ 8.12 (d, $J = 7.7$, 1H), 7.88 (d, $J = 7.6$, 2H), 7.51 (t, $J = 7.2$, 1H), 7.44 (t, $J = 7.5$, 2H), 4.68 (d, $J = 3.4$, 1H), 3.92 – 3.80 (m, 1H), 3.68 (dd, $J = 17.6$, 7.6, 2H), 3.49 (d, $J = 11.0$, 1H), 3.23 (s, 3H), 3.18 (t, $J = 9.2$, 2H). $^{13}$C NMR (101 MHz, DMSO): $\delta$ 166.5, 134.3, 131.2, 128.1, 127.5, 97.8, 72.8, 70.8, 70.3, 60.9, 54.8, 54.4. HRMS Calcd for C$_{14}$H$_{20}$NO$_6$ [M + 1]$^+$, 298.1291; found, 298.1287.

Compound 33 (43 mg, 95%) Compound decomposed upon heating, so no melting point could be obtained. $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 8.28 – 8.22 (m, 1H), 7.96 (d, $J = 8.3$, 1H), 7.93 – 7.88 (m, 1H), 7.65 (dd, $J = 7.0$, 1.1, 1H), 7.57 – 7.48 (m, 3H), 4.95 (d, $J = 3.6$, 1H), 4.22 (dd, $J = 10.7$, 3.6, 1H), 3.87 (dd, $J = 11.8$, 2.3, 1H), 3.81 – 3.70 (m, 2H), 3.60 (ddd, $J = 9.7$, 5.6, 2.3, 1H), 3.49 – 3.40 (m, 5H), 3.34 (s, 1H). $^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 172.8, 135.7, 135.1, 131.4, 129.3, 127.9, 127.4, 126.5, 126.4, 125.9, 99.9, 73.8, 72.7, 72.5, 62.8, 56.1, 55.7. HRMS Calcd for C$_{18}$H$_{21}$NO$_6$Na$^+$ [M+Na], 370.1267; found, 370.1269.

Compound 34 (42 mg, 95%); white solid; mp 156.5-157.5 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.61 (d, $J = 3.6$, 1H), 3.87 (dt, $J = 25.5$, 12.8, 1H), 3.77 – 3.68 (m, 2H), 3.61 – 3.37 (m, 4H), 3.29 (s, 3H), 2.20 – 2.13 (m, 1H), 1.66 – 1.45 (m, 3H), 1.22 (dd, $J = 7.6$, 4.3, 10H), 0.81 (t, $J = 6.8$, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 175.1, 115.3, 98.3, 72.3, 71.5, 70.7, 61.5, 55.0, 53.4, 36.3, 31.5, 29.0, 28.8, 25.5, 22.4, 13.8.
Compound 35 (43 mg, 95%); white solid; mp 122.0-124.0°C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.64 (d, $J = 3.6$, 1H), 3.94 (dd, $J = 10.3$, 3.6, 1H), 3.78 (d, $J = 3.1$, 2H), 3.65 – 3.41 (m, 4H), 3.33 (s, 3H), 2.28 – 2.07 (m, 5H), 1.91 (t, $J = 2.6$, 1H), 1.52 (ddd, $J = 22.0$, 14.4, 7.0, 5H), 1.40 – 1.13 (m, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 175.0, 98.4, 85.9, 72.7, 71.4, 70.9, 68.0, 61.7, 55.0, 53.4, 36.4, 29.1, 29.0, 28.8, 28.5, 28.3, 25.5, 18.2. HRMS Calcd for C$_{18}$H$_{31}$NO$_6$ [M + 1]$^+$, 358.2234; found, 358.2230.

Compound 36 (43 mg, 96%); white solid; mp 196.0-198.0 °C. $^1$H NMR (400 MHz, DMSO) $\delta$ 8.56 (d, $J = 13.2$, 1H), 7.34 (d, $J = 8.2$, 2H), 7.19 (t, $J = 7.8$, 2H), 6.86 (t, $J = 7.3$, 1H), 5.99 (d, $J = 8.5$, 1H), 4.58 (d, $J = 3.4$, 1H), 3.69 – 3.51 (m, 4H), 3.26 (s, 3H), 3.20 – 3.08 (m, 2H). $^{13}$C NMR (101 MHz, DMSO): $\delta$ 155.1, 140.5, 128.8, 121.1, 117.5, 98.6, 72.9, 71.8, 70.8, 60.9, 54.4, 53.9. HRMS Calcd for C$_{14}$H$_{21}$N$_2$O$_6$ [M + 1]$^+$, 313.1400; found, 313.1403.

Compound 37 (43 mg, 96%); white solid; mp 230.0-232.0 °C. $^1$H NMR (400 MHz, DMSO) $\delta$ 5.97 (d, $J = 7.8$, 1H), 5.57 (d, $J = 8.1$, 1H), 4.93 (s, 1H), 4.78 (s, 1H), 4.49 (dd, $J = 15.7$, 9.3, 1H), 3.72 – 3.54 (m, 2H), 3.50 – 3.30 (m, 2H), 3.23 (s, 3H), 3.15 – 2.97 (m, 1H), 1.79 – 1.55 (m, 4H), 1.49 (m, 2H), 1.31 – 0.95 (m, 5H). $^{13}$C NMR (101 MHz, DMSO): $\delta$ 157.5, 98.7, 72.8, 72.0, 71.0, 61.0, 54.3, 54.1, 47.7, 33.4, 33.3, 25.3, 24.4. HRMS Calcd for C$_{14}$H$_{27}$N$_2$O$_6$ [M + 1]$^+$, 319.1869; found, 319.1866.

Compound 38 (43 mg, 95%); white solid; mp 223.0-224.0 °C. $^1$H NMR (400 MHz, DMSO) $\delta$ 8.64 (d, $J = 16.6$, 1H), 8.12 (d, $J = 8.2$, 1H), 8.06 (d, $J = 7.6$, 1H), 7.87 (d, $J = 8.1$, 1H), 7.56 – 7.46 (m, 3H), 7.39 (t, $J = 7.9$, 1H), 6.65 (d, $J = 8.4$, 1H), 5.02 (d, $J = 5.3$, 1H), 4.95 (d, $J = 5.5$, 1H), 4.65 (d, $J = 3.4$, 1H), 4.55 (t, $J = 5.8$, 1H), 3.67 (dd, $J = 14.3$, 3.9, 3H), 3.54 –
3.44 (m, 4H), 3.26 – 3.11 (m, 2H). $^{13}$C NMR (101 MHz, DMSO): $\delta$ 155.5, 135.2, 133.8, 128.4, 126.0, 125.8, 125.4, 125.1, 121.8, 121.3, 115.7, 98.6, 72.9, 71.9, 70.9, 60.9, 55.3, 54.4, 54.2. HRMS Calcd for C$_{18}$H$_{23}$N$_2$O$_6$ [M + 1]$^+$, 363.1556; found, 363.1554.

**Compound 39** (42 mg, 94%); white solid; mp 185.0-186.0 °C. $^1$H NMR (400 MHz, DMSO) $\delta$ 5.61 (d, $J = 8.3$, 1H), 4.93 (d, $J = 5.5$, 1H), 4.77 (d, $J = 5.6$, 1H), 4.56 – 4.45 (m, 1H), 3.67 – 3.57 (m, 1H), 3.54– 3.26 (m, 3H ), 3.23 (s, 3H), 3.14 – 3.03 (m, 1H), 2.94 (dd, $J = 12.8$, 6.4, 2H), 1.42 – 1.13 (m, 10H), 0.84 (t, $J = 6.8$, 3H). $^{13}$C NMR (101 MHz, DMSO): $\delta$ 158.1, 98.7, 72.8, 72.0, 70.9, 60.9, 54.3, 54.2, 39.2, 31.3, 30.0, 28.5, 26.4, 22.1, 14.0. HRMS Calcd for C$_{15}$H$_{31}$N$_2$O$_6$ [M + 1]$^+$, 335.2182; found, 335.2182.

**Compound 40** (43 mg, 95%); white solid; mp 131.0-132 °C. $^1$H NMR (400 MHz, DMSO) $\delta$ 5.60 (d, $J = 8.3$, 1H), 4.92 (d, $J = 5.6$, 1H), 4.76 (d, $J = 5.6$, 1H), 4.52 – 4.47 (m, 1H), 3.67– 3.55 (m, 1H), 3.51– 3.24 (m, 2H), 3.22 (s, 3H), 3.13-3.04 (m, 1H), 2.99 – 2.88 (m, 2H), 2.73– 2.67 (m, 2H), 2.17– 2.05 (m, 2H), 1.47 – 1.12 (m, 11H). $^{13}$C NMR (101 MHz, DMSO): $\delta$ 158.1, 98.8, 84.6, 72.8, 72.0, 71.1, 70.9, 60.9, 54.3, 54.2, 39.2, 30.0, 28.7, 28.5, 28.1, 28.0, 26.4, 17.7. HRMS Calcd for C$_{18}$H$_{33}$N$_2$O$_6$ [M + 1]$^+$, 373.2339; found, 373.2344.

**Compound 41** (44 mg, 95%); white solid; mp 145.0-147.0 °C. NMR spectrum only showed the peaks between 1ppm and 2 ppm. HRMS calcd C$_{29}$H$_{59}$N$_2$O$_6$ [M + 1]$^+$, 531.4373; found, 531.4374
References


Chapter IV

Diacetylene Containing Carbohydrate Based Low Molecular Weight Gelators and the Effect of Aromatic Protecting Group at 4, 6-Position of α-D-Glucose.

Abstract: The promising results obtained from glucosamine based LMWGs encouraged us to synthesize diacetylene containing organogelators. We linked α-D-glucosamine with diacetylene group and studied gelation properties of synthesized compounds. We have synthesized various diacetylene derivatives using diacetylene containing fatty acids, these include 5, 7-hexadecadiynoic acid, 10, 12-octadecadiynoic acid, 10, 12-tricosadiynoic acid, 10, 12-docosadiynoic acid, and 10, 12-decosadiynoic acid. These compounds not only have the long carbon alkyl group, but also show polymerization under UV or heat.

In this chapter, besides the preparation of diacetylene containing glucosamine derivatives, various headgroups were also preliminarily studied in order to improve gelation efficacy. The benzyl group is usually used as protecting group at 4, 6 position of sugar head group. In most cases, it provides π-π stacking among molecules. Two additional methoxyl substituents were introduced to the phenyl ring in order to understand the influence of structure towards gelation.

Keywords: diacetylene, glucosamine, protecting group of glucose.
Introduction

Polydiacetylenes (PDAs) has been studied for more than 2 decades.\textsuperscript{1-5} It has found applications in different areas like polymer crystals, Langmiur-Blodgett films, biosensors, optical electronic devices.\textsuperscript{6-17} Our group has been studying diacetylene functional group since 2005.\textsuperscript{18,19} Diacetylene compounds can be polymerized under UV, heat, pH change as shown in Figure 4.1.\textsuperscript{20,21}

![Figure 4.1 Polymerization of diacetylene](image)

The polydiacetylenes usually show blue color. Continuous heat will turn the blue polymer into red. It is believed that this change is due to distortion of side chain (R and R’).

![Figure 4.2 The distortion of R, R’ group lead to color change](image)
Previously, we studied the 4, 6-O-benzelydene-methyl-α-D-glucopyranoside along with the following diacetylene compounds.\textsuperscript{18, 19}

Figure 4.3 The fatty acids that have been used in the synthesis of gelators by our group
The hydroxyl groups at 2- and 3-positions were esterified using the above diacetylene groups. The reaction usually yields three products like the esterification in chapter 1. The gel tests results of the esters with 10,12-tricosadiynoic, 8,10-heneicosadiynoic group, 5, 7-hexadecadiynoic group behaved well in hexane, ethanol, ethanol/water (1:1). However the minimum gelation concentrations are generally about 2 mg/mL in water. To further explore better gelator, we studied 4, 6-O-benzelidene-deoxy-α-D-glucopyranoside which can be found in second chapter. Only 10, 12-tricosadiynoyl group, 8, 10-heneicosadiynoyl group were studied, because these two diacetylenes were the ones that performed the best in the methoxy series. The gelation results showed that two dimers (structure 9, 10) are good gelators in EtOH: water (1:2). The monomers did not gel in the five testing solvents.

![Figure 4.4 The structure of dimers](image)

The study of α-D-glucosamine (Chapter 3) provided us with some very good gelators especially the 21 carbon straight chain alkyl amide and urea. Considering some of diacetylenes are very similar to the long chain alkyl group, in order to obtain diacetylene containing gelators,
we synthesized amides and ureas using α-D-glucosamine and long chain diacetylenes. The synthesis was similar to the synthesis of amides and ureas in Chapter 3. Besides the mono amides and ureas, we also studied diacetylene diacid reacting with α-D-glucosamine which yielded bis amides or bis-ureas. The gelation property was then tested.

Our group not only synthesizes different gelators but also explores the application of LMWGs. We want to study the acid stability of gels and acid trigger release system. To do this, we synthesized the following head group (11, 12). We have found out that the protecting group at 4, 6 position of head group (11, 12) is liable to acid condition, so the gel formed by gelators of 11, 12 will be subject to acid change. The synthesis is very much the same as 4, 6-O-benzyledene-methyl-α-D-glucosamine and 4, 6-O-benzylene-methyl-α-D-glucopyranoside.

![Figure 4.5 The structures of sugar head groups](image)

Different esters and amides were synthesized and tested. The amides behaved very well, but esters did not form gel in five test solvents.
Results and Discussion

The synthesis started from 4, 6-O-isopropylened-methyl-α-D-glucosamine reacting with acyl chloride or isocyanate to form amides and ureas. Because diacetylene isocyanate and acyl chloride were not commercially available, they were all synthesized in situ. Acyl chlorides of 14A, 15A, 16A, 17 were synthesized by reacting the corresponding acid with oxalyl chloride. Isocyanates of 14B, 15B, 16B were synthesized by curtius rearrangement. Because diacetylenes are light sensitive, all reactions were carried out in foil wrapped containers.

Scheme 4.1 The synthesis scheme of diacetylene amides and ureas
The products yields are shown in Table 4.1 The gel tests results are shown in Table 4.2.

Table 4.1 Yields of amides and ureas of Compound 13

<table>
<thead>
<tr>
<th>Compound</th>
<th>14A</th>
<th>14B</th>
<th>15A</th>
<th>15B</th>
<th>16A</th>
<th>16B</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield</td>
<td>82%</td>
<td>71%</td>
<td>79%</td>
<td>65%</td>
<td>78%</td>
<td>65%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Table 4.2 Library of amide and urea derivatives and their gel tests results.

<table>
<thead>
<tr>
<th>Compound</th>
<th>H₂O</th>
<th>Hexane</th>
<th>Ethanol</th>
<th>DMSO:H₂O (1:2)</th>
<th>EtOH:H₂O (1:2)</th>
<th>EtOH:HO (1:1)</th>
<th>Toluene</th>
<th>THF</th>
</tr>
</thead>
<tbody>
<tr>
<td>14A</td>
<td>P</td>
<td>I</td>
<td>S</td>
<td>P</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>14B</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>P</td>
<td>I</td>
<td>P</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>15A</td>
<td>P</td>
<td>I</td>
<td>S</td>
<td>I</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>15B</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>16A</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>16B</td>
<td>P</td>
<td>I</td>
<td>S</td>
<td>I</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>17A</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>P</td>
<td>I</td>
<td>P</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

All concentrations are in mg/mL; G, gel at room temperature; the numbers after G are minimum gelation concentrations; P, precipitation; S, soluble at~20 mg/mL; the ratio of solvents in parenthesis.
The above compounds were not tested in the usually five solvents, because we learned from Chapter 3 that protected compounds were not gelators in those five solvents. Three new solvents were tested. They are EtOH/H₂O= 1: 1, THF, toluene. All the compounds are soluble in THF and toluene. In EtOH/H₂O= 1: 1, five compounds precipitate out and two compounds are insoluble.

Five compounds were selected for deprotection. The deprotection was carried out in trifluoroacetic acid. No workup was needed. Trifluoroacetic acid, solvent and byproduct acetone were blown away under nitrogen.

![Chemical structures](image)

Figure 4.6 The synthesis of deprotected amides and ureas
The gelation property was tested in five solvents. The results are shown in Table 4.3.

**Table 4.3** The yields of deprotected amides and ureas

<table>
<thead>
<tr>
<th>Compound</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield</td>
<td>96 %</td>
<td>95 %</td>
<td>95 %</td>
<td>95 %</td>
<td>95 %</td>
</tr>
</tbody>
</table>

**Table 4.4** Library of deprotected amide and urea derivatives and their gel tests results.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hexane</th>
<th>H₂O</th>
<th>EtOH</th>
<th>EtOH:H₂O (1:2)</th>
<th>DMSO:H₂O (1:2)</th>
<th>Isopropanol</th>
<th>Toluene</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>I</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>19</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>P</td>
<td>I</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>20</td>
<td>I</td>
<td>P</td>
<td>S</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>21</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>22</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>P</td>
<td>P</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

All concentrations are in mg/mL; G, gel at room temperature; the numbers after G are minimum gelation concentrations; P, precipitation; S, soluble at~20 mg/mL; the ratio of solvents in parenthesis.
The gel test results showed that none of compounds formed gel in the five testing solvents. The solubility of the synthesized compounds was very different from that of amides and ureas from Chapter 3. The compounds from chapter 3 are insoluble in chloroform and NMR had to be taken in d-DMSO. They are good gelators in water, DMSO/water (1: 2), Ethanol/water (1: 2). However the diacetylene compounds after deprotection showed very good solubility in chloroform. Most NMRs were taken in CDCl$_3$ with only a tiny drop of d-methanol. From this we can tell that diacetylene group changed polarity significantly.

The new protecting group for 4, 6 position was synthesized by reacting 3, 4-dimethoxybenzaldehyde with trimethyl orthoformate. The product was reacted directly with N-acetyl-methyl-α-D-glucosamine.

![Scheme 4.2 The synthesis of compound 11, 12](image)
After obtaining the headgroups (11, 12), different amides and esters were synthesized. The selection of functional groups was based on previous researches.

![Diagram of ester synthesis](image)

Scheme 4.3 The synthesis of esters from compound 12

The synthesis of different esters followed the same method. The diesters and 2-monoesters are the main products. The amide formation was straightforward. The acyl chloride of compound 28 was synthesized *in situ*. The yields are shown below. The products were tested in five solvents. The results are shown in table 4.6.
Table 4.5 Yields of esters (A,B)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Total Yields</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>90 %</td>
<td>7 %</td>
<td>83 %</td>
</tr>
<tr>
<td>27</td>
<td>91 %</td>
<td>25 %</td>
<td>66 %</td>
</tr>
<tr>
<td>28</td>
<td>90 %</td>
<td>15 %</td>
<td>75 %</td>
</tr>
<tr>
<td>29</td>
<td>92 %</td>
<td>23 %</td>
<td>59 %</td>
</tr>
<tr>
<td>30</td>
<td>90 %</td>
<td>15 %</td>
<td>75 %</td>
</tr>
</tbody>
</table>

Table 4.6 Yields of Amides

<table>
<thead>
<tr>
<th>Compound</th>
<th>31</th>
<th>32</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield</td>
<td>78 %</td>
<td>72 %</td>
<td>83 %</td>
</tr>
</tbody>
</table>
Table 4.7 Gel tests results of ester and amide derivatives.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hexane</th>
<th>H$_2$O</th>
<th>EtOH</th>
<th>EtOH:H$_2$O(1:2)</th>
<th>DMSO:H$_2$O(1:2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26A</td>
<td>I</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>26B</td>
<td>I</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>27A</td>
<td>I</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>27B</td>
<td>I</td>
<td>G 20</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>28A</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>28B</td>
<td>I</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>29A</td>
<td>I</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>29B</td>
<td>I</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>30A</td>
<td>I</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>30B</td>
<td>I</td>
<td>P</td>
<td>S</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>31</td>
<td>I</td>
<td>I</td>
<td>G 10</td>
<td>G 5</td>
<td>G 5</td>
</tr>
<tr>
<td>32</td>
<td>I</td>
<td>I</td>
<td>G 20</td>
<td>G 20</td>
<td>G 20</td>
</tr>
<tr>
<td>33</td>
<td>I</td>
<td>I</td>
<td>G 20</td>
<td>G 5</td>
<td>G 3</td>
</tr>
</tbody>
</table>
All concentrations are in mg/mL; G, gel at room temperature; the numbers after G are minimum gelation concentrations; P, precipitation; S, soluble at ~20 mg/mL; the ratio of solvents in parenthesis.

Some of images from optical microscope are shown below. The gel of compound 31 consisted of long and thin tubes. This showed clearly in 500x optical micrographs. This tube is different from the one formed by compound 32. In Figure 4.9, we can see that tubes are thicker than those in Figure 4.7. Much shorter tubes were seen in Figure 4.11, this results was consistent with what we saw in Figure 3.6. It seemed that when the gel was at very low concentration, tubes or fibers were shorter and smaller.

Figure 4.7 200x Optical micrographs of gel formed by Compound 31 at 5 mg/mL in DMSO: H2O (1: 2).
Figure 4.8 500x Optical micrographs of gel formed by compound 31 at 5 mg/mL in DMSO:H$_2$O (1:2).

Figure 4.9 200x Optical micrographs of gel formed by compound 32 at 20 mg/mL in DMSO:H$_2$O (1:2).
When we compare the gel tests results of esters (26-30) with those of 4, 6-O-benzyledene-methyl-α-D-glucopyranoside esters, we didn’t see much improvement. Only one compound formed gel in water at 20 mg/mL. Precipitation can be seen in most test solvents. It can be due to the tight pack of molecules.
On the other hand, the amides behaved much better. All of them gelled ethanol, DMSO: water (1: 2), EtOH: water (1: 2). The best one formed gel at 3 mg/mL in DMSO: water (1: 2). This minimum gelation concentration was not as good as amides of 4, 6-O-benzylidene-methyl-α-D-glucosamine.\textsuperscript{22} It can be due to some distortion of π-π stacking. However none of those amides of 4, 6-O-benzylidene-methyl-α-D-glucosamine gel in ethanol,\textsuperscript{22} but the dimethoxy benzylidene acetal derivatives formed efficient gels in ethanol. The two methoxy groups on the phenyl ring could act as hydrogen bond acceptors which interact with hydroxyl group at 3 position and solvent ethanol. It can also interact with NH- from the amide group. However, it will be more conclusive if an X-ray crystal structure could be obtained.

When we look into the gelation details of compound 31, 32, 33, we can tell that amides worked much better. Each of amides formed gel in three different solvent: EtOH, EtOH:H\textsubscript{2}O (1:2), DMSO:H\textsubscript{2}O (1:2). The hydrogen bonding from amide was the main contributor of gelation.
Conclusion

The introduction of diacetylene into α-D-glucosamine significantly changed polarity of molecules. Even though none of the synthesized compound formed gel in testing solvents, it gave us an idea how diacetylene would affect polarity and gel formation and what modification may lead to effective gelators.

3, 4-Dimethoxy benzyl group was used as protecting group at 4, 6-position in α-D-glucose and α-D-glucosamine. Only one synthesized ester formed gel at 20 mg/mL in water. This is comparable to the unsubstituted benzylidene acetal series, in which the same ester none of esters formed gel. In the case of amides, the gel tests results are much better. All 3 synthesized amides can form gel in ethanol, DMSO: water (1: 2), EtOH:water (1: 2). The minimum gelation concentration reached 3 mg/mL in DMSO: water (1: 2). The two additional methoxy group definitely helped, because same amides using benzylidene acetals protecting group did not form gel in ethanol. The two methoxy groups on phenyl ring can act as hydrogen bond acceptor and interact with solvent ethanol. The headgroup 12 is worthy of further research to obtain effective organogelators.
Experimental section

General procedure for the synthesis of amide

4, 6-O-Isopropylidene-Methyl-α-D-Glucosamine (50 mg, 0.214 mmol) was dissolved in anhydrous THF with pyridine (1.07 mmol). The corresponding acyl chloride (0.214 mmol) was added to the solution, which was then stirred at room temperature for 8 hours. The reaction mixture was worked up by DCM extraction. The crude product can be purified by flash chromatography on silica gel using the solvent system hexane and ethyl acetate.

General procedure for the synthesis of ureas

4, 6-O-Isopropylidene-Methyl-α-D-Glucosamine (50 mg, 0.214 mmol) was dissolved in anhydrous THF. The corresponding isocyanate (0.214 mmol) was added to the solution, which was then stirred at room temperature for 6 hours. The solvent was removed under N₂. The crude product can be purified by flash chromatography on silica gel using the solvent system 2% methanol in DCM.

For compound 14A: 5,7-hexadecadiynoic acid (102 mg, 0.4 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.04 mL, 0.5 mmol) was added to mixture slowly and followed by 1 drop anhydrous DMF. The mixture was stirred at room temperature for 2 hours at which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of amide synthesis.
Compound 14A (131 mg, 82%); colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.92 (d, $J = 8.7$, 1H), 4.67 (d, $J = 3.8$, 1H), 4.18 (td, $J = 9.4$, 3.8, 1H), 3.90 – 3.83 (m, 1H), 3.82 – 3.68 (m, 2H), 3.66 – 3.56 (m, 3H), 3.38 (s, 3H), 2.49 (t, $J = 7.4$, 2H), 2.44 – 2.20 (m, 5H), 1.93 – 1.79 (m, 3H), 1.53 (s, 3H), 1.44 (s, 3H), 1.43 – 1.20 (m, 9H), 0.88 (t, $J = 6.7$, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.6, 99.9, 98.8, 78.1, 76.0, 74.7, 71.2, 66.4, 65.0, 63.2, 62.2, 55.2, 54.1, 35.0, 31.8, 29.2, 29.1, 29.0, 28.8, 28.3, 23.8, 22.6, 19.2, 19.0, 18.4, 14.1.

For compound 14B: 5,7-hexadecadiynoic acid (119 mg, 0.5 mmol) was mixed with triethylamine (0.13 mL, 1 mmol) and diphenylphosphoryl azide (0.21 mL, 1 mmol) in 2 mL anhydrous THF. The mixture was heated at 60 °C for 2 hours and the reaction was complete. The product was used directly following the general procedure of urea synthesis.

Compound 14B (116 mg, 71%); colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.23 (t, $J = 5.5$, 1H), 5.12 (d, $J = 8.6$, 1H), 4.67 (d, $J = 3.8$, 1H), 3.89 – 3.69 (m, 2H), 3.64 – 3.55 (m, 1H), 3.36 (s, 3H), 3.31 – 3.16 (m, 1H), 2.31 (t, $J = 6.9$, 2H), 2.23 (t, $J = 7.1$, 2H), 1.70 (p, $J = 6.9$, 2H), 1.53 (s, 3H), 1.52 – 1.45 (m, 2H), 1.42 (s, 3H), 1.40 – 1.18 (m, 11H), 0.87 (t, $J = 6.8$, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 159.0, 99.8, 99.3, 78.1, 76.2, 74.7, 71.6, 66.0, 65.0, 63.2, 62.3, 55.3, 55.2, 39.4, 31.8, 29.2, 29.1, 29.0, 28.8, 28.6, 28.3, 22.6, 19.2, 19.1, 16.7, 14.0.

For compound 15A: 10,12-octadecadiynoic acid (114 mg, 0.4 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.04 mL, 0.5 mmol) was added to mixture slowly and followed by 1 drop anhydrous DMF. The mixture was stirred at room
temperature for 2 hours at which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of amide synthesis.

**Compound 15A** (134 mg, 79%); colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.85 (d, $J = 8.6$, 1H), 4.66 (d, $J = 3.9$, 1H), 4.16 (td, $J = 9.3$, 3.9, 1H), 3.89 – 3.82 (m, 1H), 3.80 – 3.68 (m, 2H), 3.65 – 3.53 (m, 2H), 3.36 (s, 3H), 2.23 (t, $J = 7.3$, 6H), 1.69 – 1.56 (m, 3H), 1.52 (s, 3H), 1.50 – 1.45 (m, 2H), 1.43 (s, 3H), 1.41 – 1.18 (m, 11H), 0.88 (t, $J = 7.0$, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.7, 99.8, 98.8, 77.6, 77.4, 74.7, 71.3, 65.3, 65.2, 63.2, 62.2, 55.1, 54.1, 36.6, 31.0, 29.2, 29.1, 29.0, 28.9, 28.7, 28.2, 28.0, 25.5, 22.1, 19.1, 19.0, 13.9.

For compound 15B: 10,12-octadecadiynoic acid (114 mg, 0.4 mmol) was mixed with triethylamine (0.11 mL, 0.8 mmol) and diphenylphosphoryl azide (0.18 mL, 0.8 mmol) in 2 mL anhydrous THF. The mixture was heated at 60 °C for 2 hours and the reaction was complete. The product was used directly following the general procedure of urea synthesis.

**Compound 15B** (113 mg, 65%); colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.95 (d, $J = 8.5$, 1H), 4.85 (d, $J = 23.1$, 1H), 4.67 (d, $J = 3.8$, 1H), 3.90 – 3.82 (m, 1H), 3.81 – 3.67 (m, 2H), 3.63 – 3.53 (m, 1H), 3.36 (s, 3H), 3.22 – 3.05 (m, 1H), 2.23 (t, $J = 6.9$, 3H), 1.53 (s, 3H), 1.52 – 1.42 (m, 5H), 1.43 (s, 3H), 1.40 – 1.20 (m, 15H), 0.88 (t, $J = 7.0$, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 159.0, 99.8, 99.3, 77.6, 77.4, 74.7, 71.9, 65.3, 65.2, 63.1, 62.3, 55.3, 55.1, 40.6, 31.0, 30.0, 29.1, 29.0, 28.9, 28.7, 28.2, 28.0, 26.8, 22.1, 19.1, 19.0, 13.9.
For compound 16A: 10,12-tricosadiynoic acid (143 mg, 0.4 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.04 mL, 0.5 mmol) was added to mixture slowly and followed by 1 drop anhydrous DMF. The mixture was stirred at room temperature for 2 hours at which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of amide synthesis.

Compound 16A (151 mg, 78%); colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.84 (d, $J$ = 8.6, 1H), 4.66 (d, $J$ = 3.9, 1H), 4.16 (td, $J$ = 9.3, 3.9, 1H), 3.86 (dd, $J$ = 10.3, 4.3, 1H), 3.80 – 3.68 (m, 2H), 3.64 – 3.53 (m, 3H), 3.36 (s, 4H), 2.23 (t, $J$ = 6.8, 8H), 1.69 – 1.56 (m, 3H), 1.52 (s, 5H), 1.51 – 1.45 (m, 5H), 1.43 (s, 4H), 1.40 – 1.16 (m, 33H), 0.87 (t, $J$ = 6.8, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.7, 99.8, 98.8, 77.6, 77.4, 74.7, 71.4, 65.3, 65.2, 63.2, 62.2, 55.1, 54.1, 36.6, 31.9, 29.5, 29.4, 29.3, 29.1, 29.0, 28.9, 28.8, 28.7, 28.3, 28.2, 25.5, 22.6, 19.2, 19.1, 19.0, 14.1.

For compound 16B: 10,12-tricosadiynoic acid (143 mg, 0.4 mmol) was mixed with triethylamine (0.12 mL, 0.8 mmol) and diphenylphosphoryl azide (0.18 mL, 0.8 mmol) in 2 mL anhydrous THF. The mixture was heated at 60 °C for 2 hours and the reaction was complete. The product was used directly following the general procedure of urea synthesis.

Compound 16B (129 mg, 65%); colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.83 (d, $J$ = 8.5, 1H), 4.73 (s, 1H), 4.67 (d, $J$ = 3.8, 1H), 3.93 – 3.82 (m, 1H), 3.80 – 3.66 (m, 1H), 3.65 – 3.52 (m, 2H), 3.36 (s, 3H), 3.21 – 3.07 (m, 1H), 2.23 (t, $J$ = 6.9, 4H), 1.53 (s, 3H), 1.52 – 1.43
(m, 4H), 1.44 (s, 3H), 1.41 – 1.16 (m, 26H), 0.87 (t, J = 6.7, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$
158.9, 99.8, 99.2, 77.6, 77.4, 74.7, 72.1, 65.3, 65.2, 63.1, 62.2, 55.7, 55.4, 55.1, 40.7, 31.9, 30.0,

For compound 17: 10,12-docosadiyndioic acid (71 mg, 0.2 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.04 mL, 0.4 mmol) was added to mixture slowly and followed by 1 drop anhydrous DMF. The mixture was stirred at room temperature for 2 hours at which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of amide synthesis.

Compound 17 (118 mg, 76%) colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.93 (d, J = 8.7, 2H), 4.66 (d, J = 3.8, 2H), 4.14 (td, J = 9.4, 3.8, 2H), 3.87 – 3.81 (m, 2H), 3.79 – 3.68 (m,
4H), 3.64 – 3.52 (m, 4H), 3.35 (s, 6H), 2.22 (t, J = 7.2, 8H), 1.65 – 1.57 (m, 4H), 1.51 (s, 6H),
1.49 – 1.44 (m, 4H), 1.42 (s, 6H), 1.39 – 1.19 (m, 16H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.7,
99.8, 98.8, 77.4, 74.6, 71.0, 65.3, 63.2, 62.2, 55.1, 54.1, 36.5, 29.1, 29.0, 28.9, 28.8, 28.7, 28.2,
25.5, 19.1, 19.0.

Compound 18 (46 mg, 96%); white solid; mp 43.0-45.0 °C. $^1$H NMR (400 MHz, CDCl$_3$)
$\delta$ 5.81 (d, J = 9.5, 1H), 5.08 (t, J = 10.0, 1H), 4.68 (d, J = 3.5, 1H), 4.51 (dd, J = 12.2, 4.0, 1H),
4.27 (d, J = 13.4, 1H), 3.78 (d, J = 9.7, 1H), 3.58 (t, J = 9.6, 1H), 3.39 (s, 3H), 2.48 (t, J = 7.3,
1H), 2.40 – 2.18 (m, 3H), 1.90 – 1.73 (m, 2H), 1.57 – 1.45 (m, 2H), 1.44 – 1.17 (m, 12H), 0.87
(t, J = 6.7, 3H).$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 172.2, 98.5, 78.2, 75.7, 73.6, 70.0, 68.5, 66.3,
Compound 19 (46 mg, 95%); white solid; mp 51.0-52.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 6.07 (d, $J$ = 6.9, 1H), 4.67 (s, 1H), 4.03 (d, $J$ = 25.8, 1H), 3.85 (s, 1H), 3.72 – 3.55 (m, 2H), 3.38 (s, 3H), 2.23 (t, $J$ = 6.9, 6H), 1.56 – 1.45 (m, 4H), 1.42 – 1.07 (m, 20H), 0.87 (t, $J$ = 6.7, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 175.4, 135.4, 98.5, 77.6, 77.4, 75.6, 73.9, 71.3, 71.2, 65.3, 65.2, 61.9, 55.2, 53.7, 36.5, 31.9, 29.6, 29.5, 29.3, 29.1, 29.1, 28.9, 28.8, 28.7, 28.4, 28.3, 25.5, 22.7, 19.2, 14.1.

Compound 20 (43 mg, 95%); white solid; mp 44.0-46.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 6.65 – 6.50 (m, 2H), 4.60 – 4.53 (m, 6H), 3.57 – 3.31 (m, 6H), 3.25 (s, 6H), 2.28 – 2.05 (m, 6H), 1.57 – 1.33 (m, 6H), 1.32 – 1.06 (m, 20H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.5, 175.0, 127.5, 114.4, 98.2, 77.3, 77.2, 71.9, 71.5, 70.6, 65.0, 61.3, 54.8, 53.4, 36.1, 33.8, 29.4, 28.9, 28.8, 28.7, 28.6, 28.5, 28.4, 28.0, 25.4, 24.6, 18.9.

Compound 21 (39 mg, 95%); light blue solid; mp 49.5-51.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.55 (d, $J$ = 2.7, 2H), 4.50 – 4.42 (m, 1H), 3.81 – 3.39 (m, 2H), 3.35 – 3.28 (m, 1H), 3.26 (s, 3H), 3.12 – 2.90 (m, 1H), 2.14 (t, $J$ = 6.9, 7H), 1.48 – 1.09 (m, 15H), 0.79 (t, $J$ = 6.8, 5H).$^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.4, 99.0, 98.9, 77.4, 77.2, 73.5, 73.2, 71.3, 70.6, 70.4, 68.9, 66.9, 66.8, 65.1, 65.0, 61.2, 54.9, 54.0, 53.8, 40.0, 32.0, 30.8, 30.0, 29.8, 29.5, 29.0, 28.8, 28.5, 28.4, 28.3, 28.2, 28.1, 27.8, 26.6, 23.2, 21.9, 18.9, 18.1, 13.6.
Compound 22 (44 mg, 95%); light blue solid; mp 52.0-53.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.58 (t, $J = 4.0$, 1H), 3.72 (d, $J = 2.1$, 2H), 3.67 – 3.57 (m, 1H), 3.53 – 3.38 (m, 2H), 3.28 (s, 3H), 3.11 – 2.92 (m, 1H), 2.15 (t, $J = 7.0$, 6H), 1.50 – 1.10 (m, 27H), 0.79 (t, $J = 6.8$, 3H).$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 159.5, 99.0, 98.9, 77.4, 77.2, 73.4, 73.1, 71.4, 70.6, 68.9, 66.8, 66.1, 65.0, 61.4, 54.9, 54.2, 40.1, 31.7, 29.8, 29.4, 29.3, 29.1, 29.0, 28.9, 28.7, 28.6, 28.2, 28.1, 26.7, 22.5, 19.0, 18.9, 13.8.

Compound 11: N-acetal-methyl-$\alpha$-D-glucosamine (5g, 21 mmol) was mixed with compound 24 (27 mmol) which was made in situ and p-toluenesulfonic acid (0.4g, 2 mmol) in 30 mL DMF. The reaction mixture was stirred at 60°C in an oil bath for 12 hours and the reaction went completion. Solvent DMF was removed. The crude was mixed with KOH (20 g, 0.36 mol) and refluxed in 100 mL ethanol for 36 hours. Solvent was removed and reaction mixture was diluted with water and extracted with DCM 3x100 mL. The combined DCM was dried over sodium sulfate and purified by flash chromatography using hexane ethyl acetate gradient solvent system. The product was obtained as light yellow solid with a yield of 83%. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.07 – 6.99 (m, 3H), 6.88 – 6.81 (m, 1H), 5.49 (s, 1H), 4.68 (d, $J = 3.5$, 1H), 4.26 (dd, $J = 9.8$, 4.5, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.84 – 3.77 (m, 2H), 3.77 – 3.69 (m, 1H), 3.45 (t, $J = 9.2$, 1H), 3.41 (s, 3H), 2.79 (d, $J = 6.8$, 1H).$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 149.7, 149.1, 130.0, 119.1, 110.7, 109.1, 102.0, 101.3, 82.0, 71.8, 69.1, 62.5, 56.7, 55.9, 55.8, 55.4.

General procedure for ester synthesis of compound 11

Compound 12 (85 mg, 0.25 mmol) was dissolved in 2mL anhydrous THF and pyridine (0.1 mL, 1.3 mmol). Acyl chloride (0.33 mmol) was added to the mixture while it was cool in ice
bath. The resulting mixture was stirred at room temperature for 8 hour and reaction was complete. The reaction mixture was diluted with water and extracted with DCM 3x10 mL. The combined DCM was dried over sodium sulfate and purified by flash chromatography.

Compound 26A (11 mg, 7%); colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.93 (d, $J = 8.5$, 1H), 8.66 (d, $J = 8.6$, 1H), 8.30 (d, $J = 7.3$, 1H), 8.00 (dd, $J = 7.6$, 4.6, 2H), 7.92 (d, $J = 8.2$, 1H), 7.82 (dd, $J = 19.6$, 8.2, 2H), 7.65 – 7.31 (m, 6H), 7.03 (d, $J = 7.1$, 2H), 6.82 (d, $J = 8.8$, 1H), 6.23 (t, $J = 9.9$, 1H), 5.59 (s, 1H), 5.45 (dd, $J = 10.0$, 3.6, 1H), 5.29 (t, $J = 3.5$, 1H), 4.42 (dd, $J = 10.3$, 4.8, 1H), 4.16 (td, $J = 9.9$, 4.9, 1H), 3.97 (t, $J = 9.6$, 1H), 3.92 – 3.86 (m, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.50 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.7, 166.6, 149.4, 148.7, 134.1, 133.8, 133.6, 133.1, 131.5, 131.4, 131.0, 129.7, 129.3, 128.6, 128.4, 128.0, 127.5, 127.4, 126.2, 126.1, 125.6, 125.4, 124.6, 124.4, 118.7, 110.6, 109.0, 101.5, 98.1, 79.5, 72.2, 69.7, 68.9, 62.6, 55.9, 55.7, 55.6.

Compound 26B (102 mg, 83%); colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.92 (d, $J = 8.6$, 1H), 8.26 (d, $J = 7.3$, 1H), 8.05 (d, $J = 8.2$, 1H), 7.89 (d, $J = 8.1$, 1H), 7.67 – 7.58 (m, 1H), 7.58 – 7.48 (m, 2H), 7.06 (dd, $J = 6.0$, 1.8, 2H), 6.91 – 6.83 (m, 1H), 5.56 (s, 1H), 5.21 (d, $J = 3.8$, 1H), 5.15 (dd, $J = 9.6$, 3.8, 1H), 4.42 (t, $J = 9.4$, 1H), 4.35 (dd, $J = 10.2$, 4.8, 1H), 4.02 – 3.93 (m, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.82 (t, $J = 10.3$, 1H), 3.67 (t, $J = 9.4$, 1H), 3.46 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.2, 149.8, 149.0, 133.8, 131.3, 130.8, 129.7, 128.6, 127.9, 126.5, 126.3, 125.7, 124.5, 119.1, 110.7, 109.1, 102.2, 97.8, 81.5, 74.2, 68.9, 68.9, 62.1, 56.0, 55.9, 55.6.
Compound 27A (34 mg, 25%); white solid; mp 79.0-80.0 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.99 (dd, \(J = 10.6, 4.0, 4\)H), 7.56 – 7.43 (m, 2H), 7.37 (dd, \(J = 16.4, 8.3, 4\)H), 6.97 (d, \(J = 7.0, 2\)H), 6.80 (d, \(J = 8.7, 1\)H), 6.05 (t, \(J = 9.8, 1\)H), 5.52 (s, 1H), 5.26 (dd, \(J = 9.9, 3.7, 1\)H), 5.18 (d, \(J = 3.6, 1\)H), 4.37 (dd, \(J = 10.3, 4.8, 1\)H), 4.17 – 4.03 (m, 2H), 3.92 – 3.85 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.44 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 166.0, 165.6, 149.4, 148.7, 133.4, 133.0, 129.9, 129.7, 129.0, 128.4, 128.3, 118.7, 110.6, 109.0, 101.5, 97.8, 79.4, 75.5, 72.4, 69.6, 68.9, 62.5, 55.9, 55.7, 55.5.

Compound 27B (73 mg, 66%); white solid; mp 83.5-84.5 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.10 (d, \(J = 8.2, 2\)H), 7.58 (dd, \(J = 10.7, 4.1, 1\)H), 7.46 (t, \(J = 7.7, 2\)H), 7.05 (d, \(J = 6.4, 2\)H), 6.86 (d, \(J = 8.7, 1\)H), 5.54 (s, 1H), 5.08 (d, \(J = 3.7, 1\)H), 5.04 (dd, \(J = 9.5, 3.8, 1\)H), 4.41 – 4.28 (m, 1H), 4.16 – 4.02 (m, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.79 (t, \(J = 10.3, 1\)H), 3.63 (t, \(J = 9.4, 1\)H), 3.40 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 166.2, 149.8, 148.9, 133.4, 129.9, 129.7, 129.5, 128.4, 119.1, 110.7, 109.1, 102.1, 97.8, 81.5, 74.1, 68.9, 68.8, 62.0, 56.0, 55.9, 55.5.

For compound 28: 6-heptynoic acid (0.1 mL, 0.8 mmol) was mixed with 2 mL DCM and cooled in ice bath. 0.1 mL oxalyl chloride (0.08 mL, 1 mmol) was added to mixture slowly and followed by 1 drop anhydrous DMF. The mixture was stirred at room temperature for 2 hours at which time the reaction was complete. The solvent was removed under nitrogen and product was used immediately following the general procedure of amide synthesis.

Compound 28A (18 mg, 15%); colorless liquid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.02 – 6.94 (m, 2H), 6.83 (d, \(J = 8.2, 1\)H), 5.60 (t, \(J = 9.8, 1\)H), 5.46 (s, 1H), 4.95 (d, \(J = 3.6, 1\)H), 4.90
(dd, $J = 9.9$, 3.7, 1H), 4.29 (dd, $J = 10.3$, 4.8, 1H), 3.99 – 3.90 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.76 (t, $J = 10.3$, 1H), 3.63 (t, $J = 9.6$, 1H), 3.41 (s, 3H), 2.45 – 2.28 (m, 7H), 2.26 – 2.16 (m, 3H), 2.11 (td, $J = 7.0$, 2.5, 1H), 1.95 (dd, $J = 4.8$, 2.6, 1H), 1.91 (t, $J = 2.6$, 1H), 1.83 – 1.38 (m, 5H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.0, 172.3, 149.8, 149.0, 129.9, 119.1, 110.9, 109.3, 101.8, 97.9, 79.5, 77.6, 77.2, 76.9, 71.7, 69.0, 68.9, 68.8, 62.5, 56.1, 56.0, 55.6, 33.9, 33.8, 27.9, 27.8, 24.3, 24.2, 18.3, 18.2.

Compound 28B (74 mg, 75%); colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.10 – 6.98 (m, 2H), 6.88 – 6.83 (m, 1H), 5.50 (s, 1H), 4.96 (d, $J = 3.7$, 1H), 4.80 (dd, $J = 9.7$, 3.8, 1H), 4.29 (dd, $J = 10.0$, 4.7, 1H), 4.17 (dd, $J = 16.7$, 7.2, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.75 (t, $J = 8.8$, 1H), 3.58 – 3.52 (m, 1H), 3.40 (s, 3H), 2.45 (t, $J = 7.3$, 1H), 2.22 (td, $J = 7.0$, 2.6, 2H), 1.95 (t, $J = 2.6$, 1H), 1.84 – 1.71 (m, 2H), 1.64 – 1.54 (m, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.1, 149.8, 148.9, 129.7, 119.1, 110.7, 109.1, 102.1, 97.6, 81.4, 73.5, 68.9, 68.7, 68.6, 62.0, 55.9, 55.4, 33.6, 27.6, 24.0, 18.1.

Compound 29A (32 mg, 23%); colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.04 – 6.94 (m, 2H), 6.83 (d, $J = 8.2$, 1H), 5.60 (t, $J = 9.8$, 1H), 5.45 (s, 1H), 4.91 (dt, $J = 9.8$, 3.7, 2H), 4.29 (dd, $J = 10.2$, 4.9, 1H), 4.00 – 3.90 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.76 (t, $J = 10.3$, 1H), 3.62 (t, $J = 9.6$, 1H), 3.40 (s, 3H), 2.41 – 2.19 (m, 4H), 1.71 – 1.47 (m, 6H), 1.38 – 1.11 (m, 10H), 0.85 (dt, $J = 21.9$, 6.4, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.3, 172.5, 149.5, 148.8, 129.7, 118.8, 110.6, 109.1, 101.5, 97.7, 79.3, 71.4, 68.8, 68.6, 62.3, 55.9, 55.8, 55.4, 34.3, 34.1, 31.5, 31.4, 28.7, 28.6, 25.1, 24.9, 22.5, 22.4, 14.1, 14.0.
Compound **29B** (67 mg, 59%); colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.07 – 7.01 (m, 2H), 6.88 – 6.83 (m, 1H), 5.51 (s, 1H), 4.96 (d, $J$ = 3.7, 1H), 4.80 (dd, $J$ = 9.7, 3.8, 1H), 4.29 (dd, $J$ = 10.0, 4.7, 1H), 4.19 (t, $J$ = 9.5, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.86 – 3.81 (m, 1H), 3.75 (t, $J$ = 10.2, 1H), 3.56 (t, $J$ = 9.4, 1H), 3.40 (s, 3H), 2.41 (t, $J$ = 7.5, 3H), 1.71 – 1.53 (m, 4H), 1.35 – 1.24 (m, 3H), 0.88 (t, $J$ = 6.7, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.6, 149.8, 148.9, 129.7, 119.1, 110.7, 109.1, 102.1, 97.6, 81.4, 73.4, 68.9, 68.7, 62.0, 56.0, 55.9, 55.4, 34.1, 31.4, 28.7, 24.9, 22.5, 14.0.

Compound **30A** (20 mg, 15%); white solid; mp 56.0-58.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.03 – 6.95 (m, 2H), 6.83 (d, $J$ = 8.2, 1H), 5.60 (t, $J$ = 9.8, 1H), 5.46 (s, 1H), 4.94 (d, $J$ = 3.7, 1H), 4.90 (dd, $J$ = 9.8, 3.7, 1H), 4.29 (dd, $J$ = 10.3, 4.8, 1H), 3.99 – 3.90 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.76 (t, $J$ = 10.3, 1H), 3.63 (t, $J$ = 9.6, 1H), 3.41 (s, 3H), 2.41 – 2.20 (m, 3H), 1.66 – 1.51 (m, 6H), 1.36 – 1.16 (m, 7H), 0.85 (dt, $J$ = 11.2, 6.9, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.3, 172.5, 149.4, 148.7, 129.8, 118.8, 110.6, 109.1, 101.5, 97.7, 79.3, 71.4, 68.8, 68.6, 62.3, 55.9, 55.8, 55.4, 34.3, 34.1, 31.2, 31.1, 24.8, 24.6, 22.3, 22.2, 13.9, 13.8.

Compound **30B** (82 mg, 75%); white solid; mp 47.0-49.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.06 – 7.01 (m, 2H), 6.88 – 6.83 (m, 1H), 5.51 (s, 1H), 4.96 (d, $J$ = 3.7, 1H), 4.80 (dd, $J$ = 9.7, 3.8, 1H), 4.29 (dd, $J$ = 10.0, 4.6, 1H), 4.19 (td, $J$ = 9.5, 2.3, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.85 – 3.81 (m, 1H), 3.75 (t, $J$ = 10.2, 1H), 3.55 (t, $J$ = 6.7, 1H), 3.40 (s, 3H), 2.41 (t, $J$ = 6.3, 3H), 1.66 (dt, $J$ = 14.4, 7.3, 2H), 1.40 – 1.28 (m, 3H), 0.90 (t, $J$ = 6.6, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.6, 149.8, 148.9, 129.7, 119.1, 110.7, 109.1, 102.1, 97.6, 81.4, 73.4, 68.9, 68.7, 62.0, 56.0, 55.9, 55.4, 34.1, 31.1, 24.6, 22.3, 13.9.
**General procedure for synthesis of amides of compound 12**

Compound **12** (100 mg, 0.3 mmol) was mixed with pyridine (0.12 mL, 1.5 mmol) in 2mL anhydrous THF. Acyl chloride (0.36 mmol) was added to the mixture while it was cooled in ice. The mixture was stirred at room temperature for 8 hours and reaction was complete. The reaction mixture was diluted with water and extracted with DCM 3x10 mL. The combined DCM was dried over sodium sulfate and purified by flash chromatography.

**Compound 31** (164 mg, 78%); white solid; mp 74.5-76.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.05 – 7.01 (m, 2H), 6.86 – 6.81 (m, 1H), 5.84 (d, $J = 8.6$, 1H), 5.52 (s, 1H), 4.71 (d, $J = 3.8$, 1H), 4.31 – 4.18 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.82 – 3.72 (m, 2H), 3.57 (t, $J = 9.0$, 1H), 3.41 (s, 3H), 3.15 (d, $J = 2.6$, 1H), 2.25 (t, $J = 7.6$, 2H), 1.72 – 1.54 (m, 3H), 1.38 – 1.27 (m, 3H), 0.89 (t, $J = 6.7$, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.0, 149.9, 148.9, 129.9, 119.1, 110.7, 109.2, 102.0, 98.8, 82.1, 75.6, 71.0, 68.8, 62.3, 55.9, 55.8, 55.3, 54.0, 36.6, 31.3, 25.3, 22.3, 13.9.

**Compound 32** (94mg, 72%); white solid; mp 69.0-70.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.05 – 7.01 (m, 2H), 6.88 – 6.80 (m, 1H), 5.85 (d, $J = 8.5$, 1H), 5.51 (s, 1H), 4.71 (d, $J = 3.8$, 1H), 4.29 – 4.18 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.82 – 3.71 (m, 2H), 3.60 – 3.51 (m, 1H), 3.40 (s, 3H), 3.18 (d, $J = 3.1$, 1H), 2.24 (t, $J = 7.5$, 2H), 1.71 – 1.56 (m, 3H), 1.38 – 1.22 (m, 5H), 0.87 (t, $J = 6.5$, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.8, 149.6, 148.9, 129.8, 119.1, 110.7, 109.2, 102.0, 98.8, 82.1, 75.6, 70.9, 68.8, 62.3, 55.9, 55.8, 55.3, 54.0, 36.6, 31.5, 28.8, 25.5, 22.5, 14.0.
Compound 33 (114 mg, 83%); white solid; mp 81.0-83.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.05 – 7.01 (m, 2H), 6.86 – 6.81 (m, 1H), 5.85 (d, $J$ = 8.6, 1H), 5.51 (s, 1H), 4.71 (d, $J$ = 3.8, 1H), 4.31 – 4.17 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.81 – 3.71 (m, 2H), 3.60 – 3.51 (m, 1H), 3.40 (s, 3H), 3.20 (d, $J$ = 3.3, 1H), 2.24 (t, $J$ = 7.5, 2H), 1.72 – 1.58 (m, 5H), 1.37 – 1.19 (m, 5H), 0.87 (t, $J$ = 6.6, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 174.8, 149.7, 148.9, 129.8, 119.1, 110.7, 109.2, 102.0, 98.8, 82.1, 70.9, 68.8, 62.3, 55.9, 55.8, 55.3, 54.0, 36.6, 31.6, 29.1, 28.9, 25.6, 22.6, 14.0.
References


Vita

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