The Development of Novel Carbohydrate-Based Gelators and Their Applications as Advanced Soft Materials

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THE DEVELOPMENT OF NOVEL CARBOHYDRATE-BASED GELATORS AND
THEIR APPLICATIONS AS ADVANCED SOFT MATERIALS

By

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B.S., June 2013, The University of The West Indies, Mona Campus, Jamaica
M.S., May 2020, Old Dominion University, Virginia

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DOCTOR OF PHILOSOPHY

CHEMISTRY

OLD DOMINION UNIVERSITY
August 2021

Approved by:

Guijun Wang (Director)
Alvin Holder (Member)
David Courson (Member)
Jingdong Mao (Member)
Michael Kong (Member)
ABSTRACT

THE DEVELOPMENT OF NOVEL CARBOHYDRATE-BASED GELATORS AND THEIR APPLICATIONS AS ADVANCED SOFT MATERIALS

Joedian Morris
Old Dominion University, 2021
Director: Dr. Guijun Wang

Low molecular weight gelators (LMWGs) are attractive molecules that have been explored extensively due to their practical applications in many disciplines. These small molecules self-assemble forming solid-like gels via three-dimensional cross-linked networks with the solvent as the key component within the matrix. Carbohydrate-based LMWGs are small molecules that can form solid-like gels in water, organic solvents, and aqueous solutions. They have great potential to be utilized in different applications because carbohydrates are biocompatible and can be made from easily accessible and renewable resources. Designing gelators is still a challenge within the field, even though researchers have developed tools to predict gelation and other properties. Therefore, research on the structure and properties of different gelator templates remains valuable to the field.

The research in this dissertation comprises of three projects discussed in chapters 2-4. For the first project, we have studied several monosaccharide ester derivatives that can function as stimuli responsive gelators in organic solvents, water, and aqueous solutions. The results from project one demonstrated that these stimuli-responsive gelators have the potential to be utilized for dye removal and as controlled delivery carriers for various drug molecules. In the second project, we have studied a variety of glycolipid gelators containing ester, ether, and amine functional groups. Their applications for enzyme immobilization as well as the encapsulation and release of model drugs have been studied. The third project examined a series of dimeric glycolipids and
evaluated the influence of structure on the gelation properties, as well as their uses as soft materials for dye absorption studies.

Overall, several functionalized gelators and their resulting gels are stimuli-responsive to bases and lipases. Other representative gels were able to successfully encapsulate naproxen sodium as well as hydroxychloroquine sulfate and allow for their sustained release over time. The hydrogel from project two had the ability to encapsulate α-amylase and facilitated retention of its activity. This was illustrated from the recorded production of maltose by the gel throughout the experiment. In addition to that, the gels absorbed toluidine blue and rhodamine B from an aqueous solution demonstrating their potential usage in environmental remediation.
Copyright, 2021, by Joedian Morris, All Rights Reserved.
This dissertation is dedicated to my parents in Jamaica for their continuous, unwavering support throughout my entire life and their sacrifices which have led to me becoming the person I am today. I hope that they feel a sense of accomplishment through my achievements and the work that I have done over the years.
“When you practice gratefulness, there is a sense of respect towards others.” This quote by Dalai Lama absolutely represents my thoughts on constantly showing gratitude to the persons who have helped or impacted my life in any way, shape or form. I must first give God thanks for sparing my life and giving me the knowledge, wisdom and understanding to navigate the challenges of being a graduate student as well as the strength to persevere throughout the journey.

I would like to express my deepest appreciation for my advisor Dr. Guijun Wang, who accepted me in her research group and constantly provided support in the form of resources and advice throughout my time doing research. Thank you for listening to my ideas and helping me to accomplish several goals whilst challenging and encouraging me to do my best. I appreciate all the time you took to review papers and experiments and other reports whilst paying keen attention to detail, in order to provide guidance on how to improve.

I am extremely grateful for my committee members, Dr. David Courson, Dr. Alvin Holder, Dr. Jingdong Mao and Dr. Michael Kong who have provided invaluable insights, practical suggestions and helpful advice regarding my research and overall development as a scientist. Dr. Holder you were very instrumental in me applying to ODU, thank you for sharing details of the available opportunities and for being a great source for feedback and guidance throughout the years. Special thanks to Dr. Courson for welcoming me into his lab and teaching me cell culture and assay techniques that have allowed me to carryout cytotoxicity assays of some the sugar-based gelators in my research. That collaboration has widened the scope of my knowledge and given me the requisite skills to be a more well-rounded scientist. Thanks to Dr. Mao and Dr Kong, for being great sources for advice and to all my committee members, I wholeheartedly appreciate the time
you took out of your busy schedules to constantly meet with me and provide constructive feedback regarding my projects.

I have also had the great pleasure of working with the members of the Wang Lab Group, Jonathan Bietsch, Surya Adhikari, Pooja Sharma and the former group members Dr. Kristen Bashaw, Dr. Dan Wang, Dr. Anji Chen, Dr. Lalith Samankumara, Dr. Ifeanyi Okafor and Miss Consuelo Garcia. Some of you have worked with me on a few projects and have also provided encouragement throughout my time here and for that I am grateful. I must also mention the undergraduates, Abigail Olson, Cole Jackson, Anna Duffney, Logan Baker and Paige Kozlowski who I have worked with or mentored throughout my time as a graduate student, thank you for your patience and for allowing me to share in your journey by positively impacting your overall development whilst at Old Dominion University.

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I would like to recognize and thank my family members both here in the US and in Jamaica. You know all the victories and the challenges that I have faced throughout the years and I am forever grateful for your continuous support and contributions to my life; your help and assistance cannot be overestimated.

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through my graduate teaching assistantship. Thanks also to the National Science Foundation for providing funding support for my research projects and research assistantships through grants CHE #1808609 and CHE # 1313633.
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<tr>
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<tr>
<td>AFM</td>
<td>atomic force microscopy</td>
</tr>
<tr>
<td>ALP</td>
<td>alkaline phosphatase</td>
</tr>
<tr>
<td>CD</td>
<td>circular dichroism</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>CFA</td>
<td>complete Freund’s adjuvant</td>
</tr>
<tr>
<td>DAP</td>
<td>diaminopropane</td>
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<tr>
<td>DBS</td>
<td>1,3:2,4-Dibenzylidene-d-sorbitol</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
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<tr>
<td>DFO</td>
<td>deferoxamine</td>
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<td>DI</td>
<td>deionized</td>
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<td>DIEA</td>
<td>diisopropyl ethyl amine</td>
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<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
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<tr>
<td>DMSO-&lt;sup&gt;d6&lt;/sup&gt;</td>
<td>deuterated dimethyl sulfoxide</td>
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<td>DNS</td>
<td>dinitrosalicylic acid</td>
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<td>D₂O</td>
<td>deuterium oxide</td>
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<td>EG</td>
<td>ethylene Glycol</td>
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<td>EtOH</td>
<td>ethanol</td>
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<tr>
<td>Fmoc-Phe</td>
<td>N-fluorenlymethylcarbonyl phenylalanine</td>
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<tr>
<td>FT-IR</td>
<td>Fourier transform infrared spectroscopy</td>
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<td>HCl</td>
<td>hydrochloric acid</td>
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<tr>
<td>Hex</td>
<td>hexane</td>
</tr>
<tr>
<td>GNBA</td>
<td>glycosylated nucleoside based bolaamphiphile</td>
</tr>
<tr>
<td>HUVEC</td>
<td>human umbilical vein endothelial cells</td>
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<tr>
<td>i-PrOH</td>
<td>isopropanol</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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</tr>
<tr>
<td>kPa</td>
<td>kilopascal</td>
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<tr>
<td>LC-MS</td>
<td>liquid chromatography mass spectrometry</td>
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<td>LCST</td>
<td>lower critical solution temperature</td>
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<td>LMOGs</td>
<td>low molecular weight organogelators</td>
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<td>LMWHs</td>
<td>low molecular weight hydrogelators</td>
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<td>LMWGs</td>
<td>low molecular weight gelators</td>
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<tr>
<td>MeOH</td>
<td>methanol</td>
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<tr>
<td>MGC</td>
<td>minimum gelation concentration</td>
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<tr>
<td>mp</td>
<td>melting point</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>PAD</td>
<td>primary ammonium dicarboxylate</td>
</tr>
<tr>
<td>PAM</td>
<td>primary ammonium monocarboxylate</td>
</tr>
<tr>
<td>PBS</td>
<td>phosphate buffered saline</td>
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<tr>
<td>PG</td>
<td>partial gel</td>
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<tr>
<td>PXR-D</td>
<td>powder X-ray diffraction</td>
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<tr>
<td>SAD</td>
<td>secondary ammonium dicarboxylate</td>
</tr>
<tr>
<td>SAM</td>
<td>secondary ammonium monocarboxylate</td>
</tr>
<tr>
<td>SANS</td>
<td>small angle X-ray scattering</td>
</tr>
<tr>
<td>SAXS</td>
<td>small angle neutron scattering</td>
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<tr>
<td>SEM</td>
<td>scanning electron microscopy</td>
</tr>
<tr>
<td>SXRD</td>
<td>single crystal X-ray diffraction</td>
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<tr>
<td>TBO</td>
<td>toluidine blue</td>
</tr>
<tr>
<td>TEG</td>
<td>triethylene glycol</td>
</tr>
<tr>
<td>TEM</td>
<td>transition electron microscopy</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>Tol</td>
<td>toluene</td>
</tr>
<tr>
<td>UCST</td>
<td>upper critical solution temperature</td>
</tr>
<tr>
<td>UV-Vis</td>
<td>ultraviolet visible</td>
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CHAPTER 1

INTRODUCTION TO SUPRAMOLECULAR GELATORS

1.1 INTRODUCTION

Gelators are an intriguing class of multifaceted compounds that form a gel when dissolved in different solvents and have many applications across scientific fields. Scientists have investigated many classes of gelators and have found new and interesting applications for these versatile molecules; from these findings many publications have added to the wealth of knowledge surrounding these enthralling molecules. Gels are soft materials that have mechanical and viscoelastic properties in between a solid and a liquid thereby ranging from being tough and hard to weak and soft. The test for gelation generally involves dissolving a small amount of the gelator in the desired solvent or aqueous solution by heating it and then allowing it to cool to room temperature to form the gel. These molecules assemble to form a 3D network of fibers that can be on the micro or nanoscale for length or thickness, however not all gels have microstructures that are fibrillar.

Many years ago scientists reported the mechanism of gelator self-assembly shown in figure 1. It starts with one dimensional interactions that allow the molecule to assemble on the molecular level to form one 1D structures. These 1D structures then interweave to form a helical structure which could be comprised of vesicles, micelles, fibers or tapes; the tertiary structure which is next basically represents the overall network of the gel. One of the most important transitions that determine whether gelation will occur is that from the secondary to tertiary assembly; the fibers must be able to cross-link to form a continuous network with the solvent/mixture immobilized by
capillary forces or surface tension.\textsuperscript{5, 6} If this continuous network of fibers does not form, then precipitation can sometimes occur instead of gelation.

\textbf{Figure 1.} Mechanism of self-assembly.\textsuperscript{7} Adapted from ref 7, under the creative commons license. Copyright (2019) MDPI.

Gels are formed in many organic solvents or aqueous solutions by immobilizing the solvent through molecular self-assembly with the solvent as the major component.\textsuperscript{4} The enormous increase in the amount of citations related to molecular gels from 1970 to 2013 in the web of science proves how much the field of molecular gelators have grown and gained increased attention over the years in research.\textsuperscript{4} They can be classified in a few different ways based on the solvent system that they form a gel in and the interactions that govern their self-assembly. Molecules that form a gel in organic solvents are referred to as organogelators and those that form in water are known as hydrogelators.\textsuperscript{8-11} The other categories include physical or chemical gels based on the gelation mechanism or interactions that form the cross-linked network.\textsuperscript{12-14} The cardinal interactions that govern the self-assembling process for the formation of physical gels are non-covalent bonds that
include, hydrogen bonding, $\pi-\pi$ stacking, CH-$\pi$ interactions, dipole-dipole forces, Van der Waals interaction, electrostatic interactions and London dispersion forces.\textsuperscript{5,15} The latter interactions are crucial to the self-assembly of the gelator and therefore specific functional groups are generally included in the gelator molecules.\textsuperscript{5} These include but are not limited to carbohydrate molecules which are rich in O-H groups for hydrogen bonding, urea and amides, nucleobases and long chain alkanes for hydrophobic interactions.\textsuperscript{5}

Several building blocks have been utilized in the construction of gelators. Some of the reported classes include dendritic systems, carbohydrates, steroids, metallogels, fatty acids, amino acids/peptides, and others.\textsuperscript{5,9,16-18} There are also gelator compounds that consist of more than one molecule or component, which are defined as multicomponent gelators. Most of the published research on these systems have investigated two component systems, they are divided into three classes: 1) A system that consist of the gelator molecule and another component that is not capable of forming a gel; 2) A system in which both components have the ability to form a gel independently and 3) the third system comprise of two molecules that do not form a gel independently but do so when combined.\textsuperscript{6,19} The first system is normally designed when one would like to manage or change the functional properties of the gelator and the second system can have different morphology based on how they assemble on the molecular level.\textsuperscript{19} When both components can self-assemble three types of network can form on the molecular level. Both components can self-sort and give two types of fibers within the gel independently or a mixed self-sorted network, on the other hand the components can interact with each other within the fibers.\textsuperscript{19} Many of these gelator systems have been reported in the literature and have been utilized in many applications such as sensors, biomaterials and could possibly be tailored for other uses.\textsuperscript{19}
1.2 SUPRAMOLECULAR GELATORS/LOW MOLECULAR WEIGHT GELATORS

Supramolecular gelators, also termed as low molecular weight gelators (LMWGs); were defined as having a molecular weight of 300-1000 Da, but this number has extended recently to less than 3000 Da. These molecules can be characterized using several different techniques and instruments to give information relating to the molecular structure, non-covalent interactions, gelation mechanism, morphology and strength. It is very important to choose the appropriate methods for characterization and therefore, scientists need to deliberate the type of gel under investigation as well as the advantages and drawbacks of the each technique utilized in the process. Some of the techniques that will be discussed herein include but are not limited to, infrared spectroscopy, rheology, microscopy, nuclear magnetic resonance spectroscopy, circular dichroism spectroscopy, fluorescence spectroscopy and ultraviolet-visible spectroscopy.

Molecules with conjugated π-systems have very strong UV-Vis absorbance and can even fluoresce, this property of the molecule can be evaluated using fluorescence spectroscopy. Fluorescence spectroscopy can give information about molecules relating to how they behave in the presence of light and is an analytical tool for many scientific fields. The principle of fluorescence uses ultraviolet light to excite the electrons in the sample causing them to emit light that is not inevitably visible light. The intensity of the emitted light as well as the frequency can give information about the molecular structure and self-assembly with different vibrational levels. UV-Vis spectroscopy can also be used to analyze the multi-component gels by determining the type of aggregation that forms or the mechanism of gelation; whether it is through self-sorting or co-assembly. Fluorescence spectroscopy can also be utilized in the analysis of gels that have multiple chromophores to infer information on co-assembly. Absorption
spectroscopy in the ultraviolet region can also elucidate structural assembly of different gelators. Compounds that comprise of non-bonding electrons or π-systems can absorb energy in the visible or ultraviolet region; this causes the electrons to become excited and allow for transitions to higher orbitals.\textsuperscript{21} This technique as well as Infrared spectroscopy are employed with gelators to explicate the interactions that govern their self-assembly.\textsuperscript{21,24,25}

Nuclear magnetic resonance (NMR) spectroscopy is perhaps one of the oldest techniques that have been utilized to study gelators as well as several organic compounds. NMR can give detailed information about the areas on the molecule that participate in gel formation, aggregation and also the structural data.\textsuperscript{21} Several NMR techniques that have been utilized include proton NMR spectroscopy, nuclear Overhauser effect (NOE) spectroscopy, carbon NMR spectroscopy, correlation spectroscopy, diffusion ordered NMR spectroscopy as well as rotating frame nuclear Overhauser effect spectroscopy.\textsuperscript{21} Several researchers have utilized NMR to distinguish between monomers and dimeric aggregates of gelators as well as to confirm the potential of smart anion-responsive gels.\textsuperscript{26,27} Gelator molecules are generally NMR-visible before the assembly process but as soon as the fibrous network is formed, they cannot be detected anymore.\textsuperscript{23} This allows for the tracking of the gelation kinetics through the disappearance of peaks.\textsuperscript{23}

Infrared spectroscopy gives information regarding functional groups and can be employed to determine the process of gelation and hence discern the non-covalent bonds that allow for gelation to occur.\textsuperscript{21} This method can give information about the interactions such as intra- and intermolecular hydrogen bonding which can tell how a molecule or several molecules stack together to form a gel.\textsuperscript{23} Even though circular dichroism (CD) is mostly utilized to study biological
macromolecules, chiral gelators can also be characterized with this technique.\textsuperscript{28} It can be used to evaluate stereo structures as well as the interactions in chiral compounds based on how the molecules absorb right or left circularly polarized light.\textsuperscript{21, 29} A chiral molecule will generate a positive or negative spectrum because they can absorb the two polarizations differently, on the other hand; an achiral molecule will give rise to a ‘zero’ spectrum because the molecule will absorb the two polarizations similarly. Given the fact that some gelators are thermo-responsive; variable temperature CD can also give insight into the gelation process at different temperatures.\textsuperscript{29} For this to be observed, a specific amount of the gelator is examined at different temperatures. At a higher temperature, the gel dismantles and at a lower temperature it stays in the gel-form, with this, the CD band will be reduced upon heating if the gelator is chiral on the nanoscale.\textsuperscript{29} Many supramolecular gelators do have chiral centers and therefore information regarding aggregation or self-assembly can be assessed using CD.\textsuperscript{28}

The morphology of the gels is generally characterized via microscopy. Optical microscopy along with atomic force, scanning electron and transmission electron microscopy have been utilized in many papers for looking at the microstructure of gels made from various classes of compounds. Transmission electron microscopy (TEM) passes an electron beam through a sample and the picture is generated based on the association of the sample with the electrons.\textsuperscript{21} TEM is widely used to investigate not only molecular assemblies but also the structure of lipid bilayers and the technique offers very high resolution up to the sub nanometer scale.\textsuperscript{21} Optical microscopy is also used to characterize gels initially but is does not have a very high resolution which is necessary for imaging the fibrous structures.\textsuperscript{21} It is therefore normally used in conjunction with other microscopic techniques. This imaging method passes light through a sample and then the image is
detected based on the impact it has on the light source, that is, how the light is scattered, deflected or absorbed by the sample. The types of optical microscope techniques include; fluorescence, light sheet, confocal and super resolution microscopy. Fluorescence and confocal microscopy are the more common systems utilized to investigate the morphology of gels.

Scanning electron microscopy (SEM) is very similar to TEM as they both use electron beams to capture images. SEM has many advantages for studying the morphology of gelators and other self-assembled systems because of its high resolution. The technique utilizes a direct beam of electrons to scan over the sample being investigated, the signals generated form the interaction of the sample and the electrons are detected and then translated to give details regarding the surface contour or components of the sample. Atomic force microscopy (AFM) is also a common system for analyzing surfaces; it operates by using a responsive cantilever to scan a surface and give information about the structure at the nanoscale level. As the cantilever moves over the surface repulsive and attractive forces triggers it to bend and allow for it to examine the nanoscale properties of the periphery mechanically. With every technique there are disadvantages and the drawback to AFM is that the constant scanning can in fact flatten the surface of the soft material that is being probed and cause it to seem narrower and broader than it truly is. On the other hand, the benefits of AFM far outweigh the shortcomings because the method affords a three dimensional scanning profile of the surface, the sample does not require any treatment that is permanent or destructive, a wide range of samples can be used; from liquids to gaseous settings and AFM can quantify energies or forces of attraction with the network of the specimen.
According to Piepenbrock et al., the thermodynamic and rheological properties of a gel are key concepts when characterizing a gel.\textsuperscript{31} It is a quantitative method that measures the stability of a gel by its viscosity or deformation under stress.\textsuperscript{21, 31} This technique for characterization of matter also gives details regarding the mechanism for assembly and its cross-linking density or size.\textsuperscript{21} The process of acquiring data from a rheometer involves placing the sample in between two plates which apply stress to the sample by moving in an oscillatory manner relative to each other and a pressure transducer detects the strain that results.\textsuperscript{21, 31} Based on the oscillatory frequency and the magnitude of the stress; the loss modulus (Gʹʹ) which applies to the viscous behavior and the storage modulus (Gʹ) which applies to the elastic behavior can then be measured.\textsuperscript{21, 31} To fully evaluate the gel behavior, two experiments were carried out to discover its linear and non-linear response. In order to obtain the nonlinear response, the amplitude of the shear stress was varied whilst the frequency was set to a fixed value; on the other hand, the linear response was ascertained by fluctuating the frequency and fixing the amplitude stress to a small value.\textsuperscript{21, 31} In general, the structure of gels can be complex with an intricate network of assemblies; but in order for a substance to be considered a stable gel, the storage modulus (Gʹ) must be greater than the loss modulus (Gʹʹ).\textsuperscript{21, 31} Also, the elastic/ modulus (Gʹ) should be invariable with the frequency to a specific point.\textsuperscript{21, 31}

Even though many apparatus and methodologies are in place to study gelators, they are still very difficult to design for specific applications. Whilst many gels are formed via serendipity, researchers have some idea which molecules may form gels based on their structure activity studies from ongoing research. Gelators were first discovered in the late 1980’s and ever since then researchers have a constant struggle predicting which molecules will form gels or even their
properties. This challenge arises from the fact that the scope of potential molecular gelators is very wide; ranging from the smallest of molecules to the very large ones. Even with an intricate understanding of intermolecular forces that drive gel formation, it is still impossible to generalize which molecules can form gels. Still, it very logical to think that introducing functional groups that would interact to form non-covalent forces would drive or enhance gelation in a molecule. For example, the insertion of alkyl groups or long chains can increase the hydrophobic forces, adding hydrogen bond donors or acceptors and aromatic substituents that increase π-π stacking in a gelator molecule could be a rational approach for designing gelators. However, there must be a balance with all these interactions for gelation to occur and that is one aspect that makes predicting gel formation so difficult and complicated. Stereochemistry seems to aid in the gelation of molecules. Regardless of the fact that molecules do not have to be chiral to form a gel, many of the reported gelators have at least one stereogenic center. Molecular chirality enables the formation of fibers and allow for the folding of the molecule which enriches the Van der Waal’s interactions resulting in gel formation.

Scientists have come up with different approaches and techniques for judiciously designing gelators. Several years ago, in 2009, Jan H. van Esch described rules that were utilized to construct gelators in earlier times. He reported that gelators must have a component to bring about the interweaving of fibers to form a network, which means there must be robust intermolecular forces of attraction that enables the molecule to self-assembly in a 1D-dimensional array the interfacial energy between the fiber and the solvent must be dominant to hinder the formation of crystals over gelation. It has been reported that in order for gelators to be successfully devised, scientists must have an in depth understanding of the gel network at the atomic level.
instruments that have been utilized in investigating the structure of fibrous networks include but are not limited to, small angle X-ray scattering (SAXS), small angle neutron scattering (SANS) and high resolution electron microscopy. There are however, drawbacks to using these methods because they do not give detailed information at the atomic level. X-ray crystal structures can be employed for studying gelation properties at the atomic level. Scientists exploit single crystal X-ray diffraction (SXRD) and powder X-ray diffraction (PXRD) to determine the patterns in which the molecules sort themselves within a single crystal. If simulated data comparing a hypothetical X-ray diffraction pattern of a designed gelator matches the pattern of the gel itself; then it means that the molecular packing in the crystal structure is the same as the packing in the self-assembled network and therefore, scientists can conclude with high accuracy, the structure of the network at an atomic level. The other approach that many researchers have utilized for inventing gelators is known as the synthon approach which is based on crystal engineering. Later on in 1995 the model was translated in the crystal engineering field by Desiraju, who later came up with the supramolecular synthon theory. This ideology was used to explain the connection between organic compounds and their crystals through the interactions brought about by their geometrical and chemical features. Theoretically, this approach would help to pinpoint structural entities within a supermolecule that can be built rationally from several other precursor units.

Scientists such as Shinkai and his co-workers utilized this methodology by comparing the characteristics of the molecules and information that they have on the crystal structures to successfully design and predict the gelation of several compounds. The investigation of this approach led the Dastidar research group to uncover the gelation of nitrobenzene by imidazolium cyclobutene hydrogen-1,1-dicarboxylate. With this research, new doors to constructing gelator
molecules led to salt-based supramolecular synthons shown in figure 2 like, primary ammonium dicarboxylate (PAD), primary ammonium monocarboxylate (PAM), secondary ammonium dicarboxylate (SAD) and secondary ammonium monocarboxylate (SAM). The studies of Dastidar and his colleagues confirm that the supramolecular synthon technique for making and predicting gelation properties of molecules is a good approach and that one dimensional hydrogen bonding networks (HBN) are a very important components for gelation though not always required. It is important to realize that self-assembled fibrillar networks are intricate and complex. Therefore, more research including computational and experimental work that both agree are necessary in order to successfully prepare gelators and gels.

**Figure 2.** Representative schemes of the supramolecular synthons from organic salts. Adapted from ref 7, under the creative commons license. Copyright (2019) MDPI.
The other logical approach that needs to be mentioned is forming gels and gelators from supramolecular gelatons. This terminology was conceived by Liu and his colleagues in 2018 by expanding the definition of supramolecular synthons. In their review that was published in Organic Chemistry Frontiers by the Royal Society of Chemistry, they explained how that was related to the rational design of gelators. The simple definition of a gelaton states that it is a particular fragment or molecular unit from which gels or supramolecular gelators can be synthesized from. This was further expanded into two types namely, type I and type II gelatons. The concepts are very similar but just applied from a different perspective.

A type one gelaton is described as a molecular unit similar to a synthon that can be covalently linked to another component to form a gelator as shown in figure 2. The other group can be made of different functional groups attached to the gelaton by a linker. Common linkers include but are not limited to esters, ureas and amides; they are common because they provide an avenue for hydrogen bonding which is trivial for gelation. The functional groups utilized in many gelators are those having extraordinary features like coordination, fluorescence and the ability to respond to stimuli. There are many gelatons that have been studied for the design of novel gelator molecules. Glucose, gallic acid, cholesterol, amino acids and peptides are just few gelatons that have been vastly studied for the preparation of gelators. The type two gelaton primarily functions by facilitating a gelator or a non-gelator molecule to form a gel due to the fact that the gel consist of two phases, mainly the solid and the solvent. This concept is mainly used when preparing multi-component or two-component gelators and the common type two gelatons utilized the latter process are histidine, crown ether oligothiophene, lysine, N-(Pyridinium-4-yl)-napthalimide and Boc-protected dialkylglutamide. Even though tremendous research is still being done on the
design of supramolecular gelators, the approaches revised herein are a good place to start. Moving forward, the research on gelators must be more interdisciplinary in order to capture comprehensive information regarding its properties and interactions that can pave the way for designing more effective gelators with a wider application scope. At this present time, many scientists are concerned with the impact of their research on the environment. With this, they continuously develop and investigate new and interesting ways in which they can still be innovative with minimal environmental impact. The design of gelators is already a difficult task so one can imagine the added challenges for creating “green gelators”.

However, there have been reports of green gelators that were synthesized from glucose and peptide derivatives for utilization in water purification and oil spill clean-up. Amino acid derivatives also play a crucial role in the design of gelators and have been vastly studied due to their self-assembling properties. L-alanine and L-tyrosine are just a few examples of the amino acids that have been exploited and the main process of self-assemble is the hydrogen bonding that occurs between the carboxylic acid groups as well as at the amide bonds. Phenylalanine is also a very common amino acid derivative for synthesizing gelators that show gelation at very low concentrations in organic solvents at 1 wt % and have shown applications in many fields. Naturally occurring cholesterol, has also been implemented for the production of gelators with the self-assembly attributed to its hydroxyl group at carbon-3 and its polycyclic structure. Cholesterol derivatives can be modified in many ways to produce novel gelator molecules and the main method of designing these cholesterol-based gelators systems is through an aromatic group followed by a linker and then the steroidal group. Other renewable resources utilized in the
design and creation of gelators include, but are not limited to fatty acids and sorbitol derivatives. Gelator molecules and their gels have a wide variety of applications that span many different fields in science such as biomedicine, engineering and materials chemistry. They have been tremendously studied for their versatility in solving many problems. The intriguing facet of gelators that sometimes allow them to be exploited, is their stimuli-responsiveness. Stimuli-responsive gels respond to external stimuli such as pH, ligands, light, redox agents, sonication or mechanical forces, ions, temperature, enzymes, ultrasound and other factors. With this, they have been used in display devices, signal sensors, drug delivery systems, shape memory devices, molecular motors and other products. Other applications of gelators include, being employed as anti-bacterial agents, wound healing, tissue engineering, catalysis and also environmental remediation.

1.3 COMPOUNDS UTILIZED IN THE SYNTHESIS OF LMWGS

There are many classes of compounds that have been used to design and synthesize gelators whether via serendipity or by other approaches discussed earlier. As mentioned before, it is quite difficult to design and predict gelators; therefore researchers are constantly producing gelator molecules by altering known gelators in an effort to understand their properties better. With this wide variety of molecules, the applications related to supramolecular gelators are endless and there have been many reports in the literature constantly reporting new classes and applications. Gelators have been reported from a wide scope of compounds including but not limited to carbohydrates, amino acids or peptides, cholesterol, organic salts, fatty acids, nucleosides and many others. In this
section a few categories of compounds that have been employed to develop low molecular weight gelators will be discussed and their applications in different fields will be highlighted.

1.3.1 CARBOHYDRATE-BASED GELATORS

Carbohydrates are important biomolecules that are generally involved in the production of energy for the body. They are biological units that can mimic the mechanisms and structures of other biologically important macromolecules with even cell signaling properties. They have been used in supramolecular gelator systems due to their hydrogen bonding potential that is very important for the interactions in supramolecular systems. Carbohydrates are naturally occurring renewable resources that are chiral with various functional groups and the hydroxyl groups allow for sugars to form widespread hydrogen bonding interactions which allow for them to self-assemble into gel networks. Sugars are non-toxic, biodegradable, biocompatible, eco-friendly with inexpensive precursors that can be easily modified via synthetic routes to form new molecules. Subsequently, their structural diversity and chiral self-assembly can be exploited to create materials for several applications. There are many reports of proven synthetic approaches to devise numerous elementary units made of polysaccharides, disaccharides and monosaccharides for gelation. Therefore carbohydrates are easily susceptible to formulating a wide assortment of LMWGs and hence allow for their extensive research in the field as supramolecular gelators.

Many carbohydrate molecules have been altered with functional groups to rationally design more gelators and evaluate the properties that affect gelation. Some of the functional groups that have been incorporated include but are not restricted to amide, esters, ureas, triazoles, amines,
carbamates and others. Some sugars have even been modified with other molecules such as lipids, diacetylenes and with other sugars to form disaccharide-based gelators. Past research in the 1990’s by Yamasaki reported a 1,3 : 2,4-Di-O-benzylidene-D-sorbitol (DBS) compound represented in figure 3 that formed a gel in ethylene glycol with optical anisotropy in crossed polarized light.\textsuperscript{74} Shimizu and his co-worker reported a series of bolaamphiphiles with 1-glucosamide as the head group on both ends of the molecule, the structure is illustrated in figure 3. Some of the molecules self-assembled into fibrous structures and other morphologies in water, based on the length of their alkyl chain.\textsuperscript{75}

![DBS](image1)

**Figure 3.** Representative sugar-based gelators discovered in the 1990’s.\textsuperscript{74, 75}

Gelators made from isosorbide, xylitol and mannitol have also been reported in the literature. The xylitol based gelators shown in figure 4, were created specifically for oil phase gelation and the molecules were synthesized by an acid catalyzed reaction between an aromatic ketone or aldehyde with xylitol in a solvent mixture consisting of cyclohexane and methanol.\textsuperscript{76} The compounds were able to form effective gels in the aromatic solvents but were poor gelators in the paraffinic
solvents. Compounds 1a-c had the innate capacity to gel a range of crude oils with diverse densities which further substantiate their potential for cleaning up oil spills.

Figure 4. Xylitol, isosorbide and mannitol based gelators.

Monosaccharides and disaccharides have been studied immensely for their gelation properties and functions; a few representative examples with varying functional groups will be presented herein. Shinkai and his colleagues developed molecules that were generated from protecting the hydroxyl groups at position 4 and 6 on different monosaccharide derivatives with 4,6-\textit{O}-benzylidene illustrated in figure 5. The molecules formed gels in a variety of organic solvents with compounds 5 and 6 being labelled as supergelators in nonpolar solvents with minimum gelation concentrations (MGC) ranging from 0.03-0.05\% (wt/vol). Previous studies from the same authors confirmed the importance of monosaccharide molecules derivatized with 4,6-\textit{O}-benzylidene for studying the gelation properties of sugars and have emphasized the importance of hydrogen bonding in gel formation. They have also created a huge saccharide library of compounds in order to investigate gelation properties based on structure and have noted that there is a possible correlation between crystal structure and gelation ability which can be utilized for a more rational design of
This pioneering research has also impacted the work that will be presented in this dissertation, the chapters that lie ahead will shed light on the further developments and structure activity relationships that are employed to develop more ornate gelators with different functional groups and linkers.

Several carbohydrates have also been modified with ester functional groups at different positions on the sugar to generate novel gelator molecules. Wang and her colleagues have done tremendous research studying the effect of structure on gelation properties by modifying sugars at different positions to better understand gelation. They have demonstrated that placing ester groups at positions two and three of N-acetyl-d-glucosamine to generate monoesters and diesters such as

![Chemical structures](image-url)
those shown in figure 6.\textsuperscript{79,80} Many of the esters with saturated alkyl chains were not good gelators but the diester 10 was able to form a gel in EtOH:H\textsubscript{2}O (v/v 1:1) at 5 mg/mL, compound 11 formed an unstable hydrogel at 12 mg/mL whilst compound 12 successfully formed a hydrogel with a gelation concentration of 7 mg/mL.\textsuperscript{79} This study helped them to comprehend the relationship between carbohydrate structure and gelation which paved the way for the design of novel esters that were more effective gelators. Another paper published in 2019 by the same group revealed enhanced gelation of the 3-\textit{O}-esters by having an amide at position two instead of a hydroxyl group with varied R groups at position three on the sugar.\textsuperscript{80} Not only were these molecules efficient gelators, but they were able to trap a wider variety of solvents, compound 13 was a versatile gelator forming gels in pump oil, ethylene glycol, glycerol as well as mixtures of water with DMSO and ethanol.\textsuperscript{80} Compound 14 also performed well in in several solvents but the aromatic derivatives such as compound 15 were not multifaceted gelators.\textsuperscript{80}

\textbf{Figure 6.} Several monoesters and diesters previously reported.\textsuperscript{79-81}
Wang and her colleagues discovered that gelation properties can be improved in the esters by adding acetylene groups on the acyl chains. This discovery came with a few published papers from the group. The creation of gelators that comprise of diacetylene is rather interesting and fascinating because they can respond to stimuli and have different color transitions as well as change from sol to gel and vice versa, which allows for their usage in the design of sensors. The diacetylene compounds depicted in figure 7 have been able to form gels in ethanol and water mixtures as well as in pure ethanol. Even though compounds 16 to 19 were less effective gelators, they were able to polymerize when exposed to UV-light which proves they are stimuli responsive and have potential to be utilized in applications that require that phenomenon. On the other hand, the incorporation of amide and urea functionalities drastically improved the gelation properties in compounds 20 and 21. This may be due to an increase in the hydrogen-bonding donors present in the compound structure. Gelator 20 was able to form a gel in isopropanol, ethanol and toluene; its lowest concentration was in ethanol at 0.8 mg/mL. Compound 21 was also able to gel in the above mentioned solvents but also in EtOH:H₂O (v/v 1:2) with a concentration of 2.5 mg/mL. The molecules were polymerizable with color transitions under UV-light and maybe useful as sensors to identify changes within an environment.
Amide and urea derivatives without diacetylene groups have also been synthesized and exhibited gelation properties in a wider panel of solvents. Urea derivatives in general have been studied immensely as gelators and their innate gelation properties are attributed to their ability to form one dimensional hydrogen bonding arrays via the urea functional group which then allows the molecules to assembly into a 3D network.\textsuperscript{3, 85} Similarly, the amides also form hydrogen bonds which are crucial for its gelation properties.\textsuperscript{86, 87} Using the same 4,6-O-benzylidene-methyl-\(\alpha\)-d-glucopyranose headgroup, Goyal and his coworkers generated a series of amide and urea gelators with varying alkyl and aromatic groups attached.\textsuperscript{88} A few representative compounds 22-23 and 26-
27 from their series are shown in figure 8. Most of the molecules in the series formed gels in 33% aqueous mixtures of ethanol and DMSO, only a few were able to gel ethanol, water and hexane.\textsuperscript{88} The hexynyl derivative 22 was the most efficient, forming a stable gel at 0.7 mg/mL in an aqueous solution of ethanol; whilst compound 23 proved to be a hydrogelator at a concentration of 2 mg/mL.\textsuperscript{88}

![Figure 8. Sugar-based gelators containing amides and ureas.\textsuperscript{81, 88}](image)

With their continuous desire to understand the structural influence on gelation, the Wang research group set out to further evaluate the impact of the phenyl group by creating a new series of molecules similar to the previously discussed amides and ureas but with a methylene group at the 4,6 protective site.\textsuperscript{89} A few compounds 24-25 and 28-29 from the series are illustrated in figure 8.
The urea derivatives performed better in the polar organic solvents whilst the amide derivatives were better gelators in aqueous mixtures with a few forming gels in toluene.\(^9\) The gelation behavior in pump and engine oil was also assessed and the results showed that the aliphatic amide derivatives were effective gelators in the latter oils.\(^9\) On the other hand, the urea derivatives were not able to form gels in the oils, this may be due to the intermolecular attractions among the urea molecules being too strong and hence they were not able to interact with the oil.\(^9\) Compound 24 formed gels in 6 of the solvents and mixtures tested, with its lowest concentration in pump oil at 2 mg/mL.\(^9\) On the contrary, compound 25 was only able to form gels in isopropanol and aqueous solutions of DMSO and ethanol.\(^9\) Its lowest concentration of 3.3 mg/mL was seen in EtOH:H\(_2\)O (v/v 1:2).\(^9\) The urea derivatives 28 and 29 were effective gelators in ethylene glycol at 1.6 mg/mL and 3.3 mg/mL respectively.\(^9\)

Carbohydrate-based molecules with carbamate functional groups are also effective gelators because they can also form hydrogen bonds. Several O and N-linked carbamate derivatives of methyl 4,6-O-benzylidene-methyl-\(\alpha\)-D-glucopyranose have been synthesized and studied in the Wang group and a few representative compounds are depicted in figure 9.\(^0\) They hypothesized that the carbamate derivatives would perform better than their compounds containing esters at the same position of the sugar because the carboxamides offer an additional hydrogen donor for increased non-covalent interactions.\(^0\) This prediction turned out to be true as the paper reported that the carbamaes were more sturdy gelators than their ester counterparts.\(^0\) The alkyl compound 30a and the cyclohexyl derivative 30b were effective gelators in aqueous solutions of 33% DMSO or ethanol.\(^0\) In EtOH:H\(_2\)O (v/v 1:2), 30b exhibited a very low concentration for gelation at 0.91 mg/mL.\(^0\) The N-linked analogs 31a-d also produced stable gels with compound 31a forming a
hydrogel at 6.6 mg/mL. Derivative 31b also formed a hydrogel but had the lowest gelation concentration in DMSO:H2O (v/v 1:2) at 1.7 mg/mL.

Figure 9. O and N-linked carbamate derivatives of methyl 4,6-O-benzylidene-methyl-a-D-glucopyranose.81, 90

Triazoles are very common functional groups seen in low molecular weight gelators. The triazole moiety provides many advantages for the gelation properties; it can be easily accessible through click reactions, it is capable of forming π-π interactions and its structure can accommodate hydrogen bonding through it its hydrogen bonding acceptors and donor.91-93 Pathak and his coworkers created a series of phase selective arabinose based gelators with a robust triazole backbone, two representative compounds 32-33 can be seen in figure 10.94 Both 32 and 33 were
insoluble in water but were able to gel in organic solvents such as benzene, toluene, xylene and ethanol. Additionally, they were regarded as supergelators for diesel, kerosene and petrol with a MGC of 0.3% (wt/vol). Overall the latter gelators were thermoreversible and have the capability for removing terrestrial and marine oil-spills.

The Wang group have also studied the effect of the triazole group on gelation both in monosaccharide units as well as disaccharide derivatives. Their earlier research involved the incorporation of the triazole moiety at position one on the peracetylated glucosyl headgroup. Figure 10 shows a few representative compounds 34a - 34c from the series which comprised of

![Figure 10. Gelators having a triazole backbone.](image)
different groups on the triazole ring like alcohols, carboxylic acids, phenyl groups and alkanes.\textsuperscript{95} Several analogs were gelators in aqueous mixtures and polar solvents, also a hydrogel was formed by a long chain alcohol derivative.\textsuperscript{95} Compound \textbf{34c} was only able to gel in DMSO: $\text{H}_2\text{O}$ (v/v 1:1) at 10 mg/mL, \textbf{34a} formed a gel in aqueous mixtures of DMSO and water at 1:1 and 1:2 ratios whilst \textbf{34b} was a gelator only for EtOH:$\text{H}_2\text{O}$ (v/v 1:2) and DMSO: $\text{H}_2\text{O}$ (v/v 1:2).\textsuperscript{95} The dimers that were synthesized with long alkyl chains between the triazole groups were also effective gelators for some polar solvents like ethanol and isopropanol as well as aqueous mixture of water with ethanol or DMSO.\textsuperscript{95}

Over the years working with glucose-based gelators, the same group realized that D-glucosamine molecules performed better as opposed to D-glucose molecules with the same modifications.\textsuperscript{96} With that, they generated a new series of peracetylated D-glucosamine triazole derivatives in order to evaluate the effect of structure on gelation properties, a few compounds from the series can be seen in figure 10 \textbf{35a-c}.\textsuperscript{96} In general, they found that the less polar aliphatic derivatives were more effective gelators.\textsuperscript{96} They obtained several successful hydrogelators from the series with two from the dimers that had long chain spacers between the two triazole moieties.\textsuperscript{96} Compounds \textbf{35a-b} were two of the hydrogelators that also gelled in aqueous solutions of DMSO and ethanol.\textsuperscript{96} Derivative \textbf{35c} was not capable of forming a gel in water but did so in aqueous DMSO and ethanol solutions. Overall, the glucosamine triazole gelators were better hydrogelators than the glucose-based triazole and typically had lower gelation concentrations for the monomers.\textsuperscript{95, 96}

Since the Wang research group studied the effect of the triazole moiety at position one on glucose and glucosamine; they thought it would be interesting to assess the introduction of the triazole
group at the 2-acyl position on glucosamine as seen in compound 36 in figure 11. In their report, they conferred that alteration could result in stronger gels possibly due to additional hydrogen bonding from the amide and π-π stacking by the triazole rings. Their hypothesis proved to be true with the series producing eleven effective hydrogelators at low concentrations of 0.15-1.0 wt %; most of the analogs were also good gelators for aqueous solutions containing 33% ethanol or DMSO. The derivatives 36a-c were all good gelators in aqueous mixtures of water with ethanol or DMSO at a ratio of (1:2) with the propyl compound 36a being the best gelator in water at a concentration of 1.5 mg/mL. The D-glucosamide triazole compounds in the series confirm that their structure is effective for designing soft materials based off sugars.

Figure 11. Other reported gelators with a triazole backbone. 81, 91, 97
Additionally, another research group headed by Ram Sagar in India, also investigated the effect of triazole groups on N-acetylglucosamine. Most of the previously reported sugar-based gelators for crude oil separation have base or acid sensitive groups which are not suitable for that application. In order to overcome this challenge, they postulated that synthesizing a series of N-acetylglucosamine derivatives modified with the triazole functional group at position six would yield more stable carbohydrate gelators for the aforementioned purpose. The series consisted of various aromatic and aliphatic derivatives on the triazole ring and a few compounds 37a-c are portrayed in figure 11. They were superb gelators in non-polar solvents like mesitylene, toluene, xylene and benzene with concentrations ranging from 0.14-0.92% N-acetylglucosamine (wt/vol). Of all the compounds in the array, 37b was the best performing gelator with a low MGC of 0.14% (wt/vol) in mesitylene. The latter gelator formed a gel in a shorter time frame than the others and demonstrated excellent potential for the recovery of crude oil and the removal of synthetic dyes.

Whilst monosaccharides have been immensely studied for their gelation properties, disaccharides and other oligosaccharides are seldomly studied. This dissertation is mainly focused on monosaccharide gelators, but it is important to highlight that oligosaccharides are also being studied for their gelation properties. A brief overview of a few disaccharide-based gels will be featured herein. In 2012 a Japanese group reported amphiphilic disaccharides derivatized with glycine connected to azobenzene (figure 12). The goal was to create glycoclusters that can self-assemble and with the capability to recognize specific proteins. They specifically engineered the molecules utilizing azobenzene because it is hydrophobic, it can form photoisomers and have strong π-π stacking from the trans-azobenzene group that could possibly result in efficient gelators. The molecules were soluble in polar aprotic solvents but were insoluble in non-polar
solvents. Compound 38b did not form a stable hydrogel, but 38a and 38c which were thermally reversible and stable as a gel for up to 10 months. Derivative 38c had the best gelation performance with a low concentration of 1.0 mg/mL in water. They were then tested for their ability to bind lectins and it was further concluded that the compounds are successfully recognized by lectins and hence can be applied in the framework of scaffolds for cell culture by way of glycoreceptor-mediated cell signaling.\textsuperscript{24}

![Figure 12. Molecular structure of amphiphilic azobenzene disaccharide gelators.\textsuperscript{24}](image)

Other disaccharides reported in the literature include compound 39 in figure 13 that was synthesized from lactobionic acid using three simple steps for the synthesis.\textsuperscript{98} The major aim of the research was to generate low molecular weight gelators from carbohydrates using simple and facile reaction schemes and investigate their application for cell culture.\textsuperscript{98} The molecule formed a shear-induced thixotropic hydrogel and had convoluted gelation characteristics due to polymorphism at various concentrations.\textsuperscript{98} Polymorphism has been reported by many as one of the major problems that affect reproducibility of gel formation and is believed to be attributed to the
rigid triazole spacer having two amide bonds which cause the molecule 39 to bend resulting in different conformations.\textsuperscript{98,99,100} Even though the application of the gel as a scaffold for cell culture indicated a reduction in the cell biocompatibility, it is still important to note that the pathway for gelation can be controlled to give different morphologies.\textsuperscript{98}

Figure 13. Dimeric sugar gelators.\textsuperscript{81,98,101}

In order to comprehend gelation properties of having an additional saccharide on the sugar units in their lab, the Wang group set out to produce disaccharides with the triazole system based on their previous research with peracetylated glycosyl triazole lipids that proved to be successful gelators.\textsuperscript{101} In their study they added lactose (40) and maltose (41) to the glucosyl triazole
headgroup and then modified it with different groups on the triazole component to give a series of compounds including \(40a-c\) and \(41a-c\) which are shown in figure 13.\(^{101}\) Of all the lactosyl derivatives only \(40c\) was able to form a gel in EtOH:water (v/v 1:1) and DMSO:water (v/v 1:1); this may be attributed to the phenyl group’s additional \(\pi-\pi\) interactions allowing for the molecule to self-assemble into fibers.\(^{101}\) All the other lactosyl containing disaccharides were insoluble in hexane, but soluble in isopropanol and ethanol. They formed a precipitate in water and were either soluble or precipitated in aqueous solutions of water with DMSO or ethanol.\(^{101}\) On the other hand, the maltose-based disaccharides \(41a-c\) were much better gelators that formed gels in aqueous solutions of water with DMSO or ethanol as well as isopropanol and ethanol.\(^{101}\) Compound \(41b\) was an efficient gelator in aqueous solutions of water with DMSO or ethanol with concentrations ranging from 2.0-5.0 mg/mL, whilst the phenyl derivative \(41c\) formed a stable gel in ethanol as well as the aqueous solutions with concentrations ranging from 2.0-6.7 mg/mL.\(^{101}\) Overall, the group concluded that the disparities with the gelation properties of the disaccharides could possibly be associated with the structural pattern of the sugar groups.\(^{101}\)

Consequently, other disaccharides having the triazole moiety have been found to be excellent and consistent gelators. A research group from Europe also explored hydrogels that were classed as glycoamphiphiles with a polar disaccharide headgroup and found that the gels exhibited supramolecular chirality with a twisted ribbon morphology.\(^{102}\) The synthesized compounds can be seen in figure 14, compound \(43\) was previously synthesized but was included in the report for comparison. Derivative \(43\) was a maltose-based triazole gelator with a lipid chain of up to 16 carbons, it formed a gel in water at a concentration of 1 wt %.\(^{103}\) Since it was the only hydrogelator in the series, they modified the compounds in a new report to understand the structural relationship
with gelation properties and that yielded compounds 42 and 44 which had lactose and cellobiose respectively as the polar headgroup. They were able to gel water as well with a MGC of 0.5 wt % for 44 and 1 wt % for 42; the gels displayed a mesomorphic lamellar fluid state and were thermally reversible. Their study contributes to the understanding of the structural impact on gelation for carbohydrate-based supramolecular amphiphiles.

![Diagram of glycoamphiphiles synthesized from disaccharides](image)

**Figure 14.** Glycoamphiphiles synthesized from disaccharides.

### 1.3.2 AMINO ACIDS AND PEPTIDE-BASED GELATORS

Amino acids, peptides and peptidomimetics have long been studied and immeasurably applied for the synthesis of gelators and by extension gels due to their biological activities and
Due to their structural properties, amino acids and peptides can form intertwined networks via interactions such as hydrogen bonding, aromatic stacking, electrostatic interactions and hydrophobic interactions. Another reason for the increased research on peptide-based gelators is as a result of well-established methods for the synthesis of peptides such as solid phase peptide synthesis that can be carried out in a speedy manner by utilizing both biological and chemical reactions to amend the structure. Also, peptide-based low molecular weight gelators provide a basic system that can be used to examine the self-assembly of such structures. Since peptides are made from amino acids, the gelators that are created from these compounds are similar in terms of their properties. Herein, a few examples of gelators made from amino acids, lysine, alanine, glutamic acid and a few others will be described and then a brief review of the peptide-based gelators will be presented.

The most common amino-acids that have been used for the fabrication of gelators are L-amino acids, they are relatively non-toxic, environmentally friendly, low cost, commercially available and biodegradable molecules. The L-amino acids that have been studied as scaffolds for low molecular weight gelators are, L-alanine, L-serine, L-lysine, L-isoleucine, L-glycine, L-phenylalanine, L-valine, L-leucine, L-tyrosine and L-tryptophan. The first gelator of L-lysine was reported by Amis and his co-worker as a N^ε-lauroyl-N^α-stearylaminocarbonyl- L-lysine ethyl ester. They formed gels in various solvents such as polar solvents, ketones, vegetable and minerals oils, cyclic ethers, alcohols, alkanes, esters and aromatic solvents. With this wide scope of gelation solvents, the gelator was regarded as a super organogelator. Suzuki and Hanabusa have written a detailed review of lysine based gelators with an explanation of their synthesis and gelation properties. They described two component gelators as well as both
negatively and positively charged lysine derived gelators that formed hydrogels and organogels with different uses.\textsuperscript{109}

Derivatives of alanine and phenylalanine have been studied frequently and proved to be very effective gelators.\textsuperscript{5, 50} In 2001, a phase selective gelator was made from an alanine derived amphiphile, to be exact \textit{N-lauroyl- L-alanine}.\textsuperscript{111} It formed gels in a variety of organic solvents, SEM and FT-IR were used to evaluate its gelation characteristics and morphology.\textsuperscript{111} Another amino acid useful for the design of gelators is phenylalanine. This neutral amino acid has an aromatic side chain that is hydrophobic and so it is categorized as being a non-polar amino acid.\textsuperscript{50} Most of the gelators that are prepared from phenylalanine came about from changes made to the N or C terminal of the molecule.\textsuperscript{50} To this date, phenylalanine is the only amino acid that has demonstrated gelation without any changes made to the N-terminus.\textsuperscript{112} Also, phenylalanine was proven to form a selectively stable metallogel with Copper (II) ions with various combinations of L-phenylalanine and D-phenylalanine. However, when the enantiomeric excess was below 30\% the system was not able to form a gel.\textsuperscript{113} A large amount of gelators have been synthesized and analyzed from modifications to phenylalanine. A review article published in 2018 by Das and coworkers, gave a detailed assessment of phenylalanine derived gelators.\textsuperscript{50} A few representative molecules \textit{45-49} can be seen in figure 15. The amino acid has been altered with carbamates, azo compounds, amides, esters, diamides, amines and acids to form effective gelators.\textsuperscript{50} The gelators formed physical gels that had to the potential be employed as materials for the removal of environmental contaminants, sensors, tissue engineering and nanodevices.\textsuperscript{50}
Alkyl groups have been added to glutamic acid to give a double-long chain-terminated hydrogelator, and it has shown favorable solubility in solvents such as hexane and water where it formed gels. Other amino acids have been modified with alkyl chains, aromatic substituents and salts, to form effective gelators in many different solvents. Peptides and peptidomimetics have also been explored as gelator molecules. They can be produced in large amounts via basic chemical reactions and hence allows for them to be studied widely. Oligopeptides have been constructed using different series of amino acids which resulted in stable gels. For example, a pentapeptide was created from the amino acid sequence Boc-Leu-Val-Aib-Phe-Aib-OMe, it was found to be an effective gelator. X-ray crystallography data demonstrated that the gel was non-porous with a helical structure due to inter- and intramolecular hydrogen bonding interactions. The gel was also competent at removing dyes from contaminated water and adsorbing I₂. Other peptides have been fabricated with the addition of groups such as naphthalene, pyridine, F-moc and pyrene.
to form gelators.\textsuperscript{105} The examples of naphthalene derivatives were good hydrogels with superhelical fibers and a cytotoxicity assay demonstrated that they are also biocompatible.\textsuperscript{116}

Peptide analogs derived from pyridine-2,6-dicarboxamide that formed gels in organic solvents have also been reported in the literature.\textsuperscript{117} Peptidomimetics are regarded as molecules that are made to imitate a natural protein or peptide but can still have biological activity.\textsuperscript{118} These types of molecules have also been studied for their gelation properties and applications. Tomasini and his colleagues have published a detailed review of several peptidomimetics that behave as gelators with most being synthesized with modifications consisting of peptide amphiphiles, cyclobutane and some having C3-symmetry with cyclohexane in the center.\textsuperscript{105} The morphology of the gels formed by many peptides and peptidomimetics happen to be helical or sheet-like assemblies that are supported mainly by hydrogen bonds.\textsuperscript{105}

1.3.3 CHOLESTEROL AND OTHER STEROID-BASED GELATORS

Steroids like carbohydrates, are naturally occurring molecules that can be easily accessed and readily modified with functional groups to change the polarity profile, making them desirable building blocks for the generation of new supramolecular gelators.\textsuperscript{119} Their molecular architecture encompasses a tetracyclic ring complex with the attachment of various functional groups, some common steroids include cholesterol and bile acids.\textsuperscript{119} Cholesterol represents the general structure of most steroidal compounds which have found applications in many areas such as, biology, electronics, optics, catalysis and mechanics due to their distinctive chemical and physical properties.\textsuperscript{119} Many derivatives of steroids have been investigated as low molecular weight gelators and a few examples will be highlighted here.
Some of the early reports of hydrogels made from bile salts date back to the early 1950’s whereby a hydrogel formed by sodium deoxycholate was discovered to have a helical network.\textsuperscript{120} From then on Maitra and his colleagues have done tremendous research on gelators derived from bile salts and have contributed immensely to the literature regarding steroidal gelators.\textsuperscript{119} On the other hand, the first report of a cholesterol-based gelator was in the late 1980’s whereby Weiss and his team investigated an organogel that was made from cholesteryl 4-(2-anthryloxy)butyrate (CAB).\textsuperscript{121} Since then, research incorporating cholesterol-based gelators have garnered much interest with many of them having a wide variety of applications.\textsuperscript{122} The method for designing these steroid-based gelators was formulated by Weiss and his team whereby, the steroidal group (S) was attached to an aromatic moiety (A) via a functionalized linker (L) giving rise to ALS type gelators.\textsuperscript{121, 123-125} This architecture led to the creation of molecules that were effective gelators and sometimes gelation could be predicted.\textsuperscript{121, 123, 124} In recent times, many researchers have adopted this design and have also introduced novel dimeric forms of steroidal gelators with the general structure, LS\textsubscript{2} and A(LS)\textsubscript{2}.\textsuperscript{119}

There are reports of organogels synthesized from a cholesterol-based perylene scaffold that have visible-light-harvesting capabilities resulting in luminescent soft materials.\textsuperscript{126} Incorporating the perylene molecule into the gelator structure enables it to adopt some of the electrochemical and optical characteristics that are innate to perylene, whilst the cholesterol moiety would allow for the one dimensional self-assembly of the gelator.\textsuperscript{126} Figure 16 depicts the gelators synthesized in this series and 50a-c were not gelators in the tested solvents. However, 50d was able to form a partial gel in solvents like toluene, benzene and p-xylene; and insoluble in polar alcoholic solvents such as ethanol, butanol, propanol and methanol.\textsuperscript{126} The compound 50d formed transparent gels in
mixed p-xylene with several alcohols, which is crucial for its photochemical properties at a range of gelator concentrations.\textsuperscript{126} In a mixture of 1-propanol and xylene (v/v 1:3), at a concentration of 0.5\% (wt/vol) (3.8 mM), the gel was very stable even at high temperatures (>80 °C) before turning to a solution.\textsuperscript{126} Overall, this cholesterol-based gelator formed an efficient gel that has the potential to be used in systems such as fluorescence sensors, signal amplifiers and other devices.\textsuperscript{126}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{cholesterol-based-gelators.png}
\caption{Representative cholesterol-based perylene derived gelators.\textsuperscript{126}}
\end{figure}

Chemoresponsive cholesterol-based gelators have also been generated via the addition of the maleimide group (51) as seen in figure 17.\textsuperscript{127} The researchers sought to develop a gelator that had a cholesterol group to influence gelation and the maleimide unit for its chemoresponsive abilities.\textsuperscript{127} Under basic conditions, the maleimide group on compound 51 reacted with thiols to form 52a-b which are the Michael adducts.\textsuperscript{127} The gelation ability of the molecules were tested and all three formed gels in cyclohexane and triethylamine.\textsuperscript{127} Compounds 51 and 52a were able to form gels in ethanol whilst only 52a-b were able to gel n-hexane. The best performing gelator was 52b with a MGC of 8 mg/mL in n-hexane.\textsuperscript{127} The gel formed by 51 was able to transition from
the gel to solution phase in 2 h after being treated with n-hexylthiol and triethylamine.\textsuperscript{127} The design of these gelators gives insight into the preparation of responsive soft materials that can be utilized as sensors and as a method for drug delivery.\textsuperscript{127}

![Chemical structures of cholesterol-based chemoresponsive gelators.](image)

**Figure 17.** Chemical structures of cholesterol-based chemoresponsive gelators.\textsuperscript{127}

As mentioned earlier, dimeric forms of steroidal gelators have been studied and examples include compounds 53-55 (figure 18). These gelators were synthesized with cholesterol having the general structure of A(LS)\textsubscript{2} with an aromatic center (A), attached to two steroidal groups (S) via two functionalized linkers (L). Compound 53, characterized by the benzene center was synthesized along with its para and ortho derivatives by Fang and his colleagues in 2008.\textsuperscript{128} The meta (53) and
para substituted molecules were more efficient gelators than the ortho derivative with compound 53 forming a spontaneous thixotropic gel in xylene at room temperature.\textsuperscript{128} Later on, researchers adopted the same design but introduced the pyridyl moiety at the center (54-55) in order to create gelators that could possibly chelate metals.\textsuperscript{129} They were successful in their endeavors as compound 55 was a good gelator for alcohols, solutions of DMF and water with up to 30\% of water and a few other solvents, but 54 was a poor gelator.\textsuperscript{129} Compound 55 was able to form complexes with Ag(I) and Zn(II) ions; also the metallogel containing silver was able to form silver nanoparticles \textit{in situ} and as a result may have to the potential to be utilized in pharmaceutical applications.\textsuperscript{119}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Figure_18.png}
\caption{Cholesterol-based gelators with an aromatic center.\textsuperscript{128, 129}}
\end{figure}
Fang and his co-workers reported cholesterol derivatives designed with amino acid spacers that were believed to enhance the hydrogen bonding capacity and serve as a means to understand the relationship between structure and gelation properties. They also wanted to study the potential of cholesterol-based gelators to form ionogels in ionic liquids (ILs) which were under investigated at the time. Two of the representative compounds 56a-b from the series are depicted in figure 19. Compound 56b with D-phenylalanine in its structure was the best performing gelator forming gels in four of the ionic liquids tested which were imidazolium salts. On the other hand, compound 56a only formed gels in two of the ionic liquids; there studies demonstrated that slight changes in the gelator structure have a huge impact on the gelation properties with the aromatic ring from the amino acids playing a major role in the efficiency of gelation.

The cholesterol-coupled diaminomalenonitrile-based gelator 57, turned out to be a good gelator in dimethylformamide (DMF) and water at a ratio of 1:1 as well as in 1,2-dichlorobenzene. The DMF:H₂O gel was the most effective and was thermally reversible and stimuli responsive. The gel was able to sense hydrazine, Hg²⁺ and Cu²⁺ due to their interaction with the malenonitrile moiety which was visually observed in a gel-sol transformation. In addition the gel was also able to absorb cationic dyes in water which further demonstrates the wide scope of applications for gelators derived from cholesterol. Photoresponsive azobenzene gels have also been reported with a cholesterol backbone. The azobenzene derivative 58 is a great example of a photoresponsive cholesteryl based organogel. It formed gels in 1-butanol, isopropanol and ethanol with all the gels experiencing the gel-sol transition upon irradiating with UV light due to the cis-trans and trans-cis photo-isomerization of the azobenzene moiety.
Bile acids and salts are also common amphiphilic steroids that have been evaluated for their gelation potential. They occur naturally in our bodies and form micelles to assist with the digestion of fat. They have since been modified in many different ways to produce gels that can interact with metals and anions for various applications. A few recent examples of gelators from bile salts are depicted in figure 20. Compounds 59 and 60 represent some of the bile acid hydrazide derivatives that have been produced using various hydrazides and cholic acid. The best performing gelator turned out to be derivative 59 which formed gels in all of five of the ten tested...
solvents, whilst compound 60 only formed gels in three solvents. Intriguingly, the gels could undergo the gel to sol transition by heating, shaking energetically and by sonicating. The gelators 61 and 62 were similarly developed from bile salts but have the potential to sequester carbon dioxide. At a concentration of 3 wt %, compound 61 can form a hydrogel without carbon dioxide present but at lower concentrations like 2 wt %, carbon dioxide is necessary for the establishment of a stable gel. On the other hand, compound 62 will only form a gel after carbon dioxide is bubbled through the solution and it as also discovered that the stability and other mechanical properties of the hydrogels were influenced by the concentration of carbon dioxide.

Figure 20. Bile acid-based gelators.
1.3.4 SALT-BASED GELATORS/ IONOGELS

Low molecular weight gelators are being created from organic salts and can also form gels in ionic liquids creating what is referred to as ionogels. The discovery of organic salts as gelators began with the Dastidar research group in the early 2000’s. The scientists were investigating the X-ray crystal structure of some new organic salts to understand their interactions in the development of solid-state materials. However, upon recrystallization of the imidazolium hydrogen cyclobutane-1,1-dicarboxylate salt in nitrobenzene, the compound formed a gel instead of crystals. This discovery gave birth to salt-based gelators and has led to the widespread investigation of gelators from organic salts.

Several features have allowed for salt-based gelators to become quite important in the field as well as for their utilization in a wide variety of applications. Researchers have found that the energy associated with the charge-assisted hydrogen bonding that is present in organic salts is approximately 40-190 kJ/mol. This bond is very strong and allows for more stable gels in comparison to the normal hydrogen bond whose energy approximation is 10-65 kJ/mol. This increased stability feature, gives salt-based gelators the advantage over other gelators for real world applications where strength is important. Subsequently, there is an unlimited number of acids and bases commercially available for employing salts as gelators so a combinatorial library can be established. Additionally, organic salt formation is a simple reaction that can be easily purified to give high yields of many salts in a short time period of time. Scientists have also noticed that the supramolecular synthon approach is very useful for designing these types of gelators. This is due to the fact that there should be a 1D hydrogen bonding network present in the
gelator structure in order for it to form one-dimensional fibers which have a higher probability of forming a gel and this can be achieved through the crystal engineering method.\textsuperscript{7}

Some of the early organic salts that were reported as low molecular weight organogelators were those generated from benzylammonium cinnamate salts, some of which are shown in figure 21. Compound \textbf{63} was able to form a spontaneous gel in ethyl acetate when sonicated.\textsuperscript{138} Gelators \textbf{64-66} were among the best performing form the series that was created, they were able to gel 10 or more of the solvents tested at very low concentrations.\textsuperscript{138} These results reveal the capabilities of exploiting the supramolecular synthon approach for designing gelators from organic salts.\textsuperscript{138} There have also been reports of ionogels with high electrical conductivity which were formed from host guest interactions among ionic liquids and β-cyclodextrin.\textsuperscript{139} Other ionogels developed from polycarboxylate imidazolium salts proved to be efficient gelators for ionic liquids more so than the conventional solvents, with thermoreversible properties.\textsuperscript{140} The gels were also very good at absorbing cationic dyes form waste water with self-healing abilities.

![Figure 21. Representative benzylammonium cinnamate salts.\textsuperscript{138}](image-url)
In the spring of 2019, Dastidar and his colleagues reported a new series of organic salts synthesized from flufenamic acid, using the synthon approach. A few presentative compounds from the series are shown in figure 22, majority of the salts were able to form gels with compounds 67-69 forming hydrogels and compounds 69 and 70 forming gels in methyl salicylate. Gelators 67-70 were tested further for their biomedical applications and compound 70 was found to have anticancer and anti-inflammatory properties. The studies illustrated the potential of 70 to be utilized in self-drug delivery.

![Figure 22. Gelators based on PAM Salts.](image)

### 1.4 STIMULI RESPONSIVE LMWGS

One of the main facets of gelators that allow for them to be utilized in many applications is the fact that they can respond to different stimuli. The various types of stimuli can be chemicals, physical forces, or biological influences which result in the transition of the gel into a solution.
phase due to disruption of the interactions within it. A stimuli responsive material is defined as a gel that has one or more units that is spectroscopically active and can act as a receptor. Several stimuli that are heavily investigate include but are not limited to, temperature, light, enzymes, pH, mechanical forces, redox reactions and ions (anions and cations). The introduction of these stimuli to a gel, changes the physical properties and alter the self-assembled fibrillar network which means that in order to be a responsive material, the responsive component within the gel network must be actively involved in the self-assembling process. In this section a few examples of various stimuli responsive materials will be discussed briefly.

1.4.1 TEMPERATURE RESPONSIVE GELATORS
Echeverria and her colleagues mentioned that temperature is a very common stimuli to be investigated since it can be regulated easily for biomedical uses. Many supramolecular gels often form at high temperatures and are generally stable at low temperatures; these characteristics allow for them to be utilized in several applications where temperature is a stimuli. The critical temperature is denoted as the point at which a response is detected whereby a phase change occurs between the gelator and the solvent and the phase of one is enhanced in the system. With this, Koetting noted that thermoresponsive materials can be divided into negative systems that have a lower critical solution temperature (LCST) and positive systems that have an upper critical solution temperature (UCST). Both polymeric and supramolecular gels have temperatures at which they transform from a gel to a solution. An enormous number of gels with the latter characteristics have been reported in the literature but only a few examples will be discussed herein.
Kuddushi et al. reported a salt-based low molecular weight gelator made from cetylpyridinium chloride and sodium salicylate as shown in figure 23. The salt was able to form an ionogel outside of its critical gelation concentration of 4.70% (wt/vol) in water. At 15 °C an opaque micellar solution was obtained but, as the temperature was slowly increased to 25 °C; a clear gel was observed.\textsuperscript{145} The gel reverted to its opaque appearance after the temperature was reduced back to 15 °C. The transparent hydrogel formed by compound 71 had long intertwined fibers throughout its network. Their studies showed that, upon increasing the temperature, the water gets released from the gel network and disrupts the insoluble fibers which then form cylindrical structures that allow for the transformation of the gels physical appearance to clear.\textsuperscript{145} The hydrogel was also capable of encapsulating a known anticancer drug, imatinib mesylate. Drug release was investigated at pH 10, 7.4 and 5; with the temperature at 15, 25 and 37 °C. Imatinib mesylate was slowly released from the ionogel at pH 10 and 7.4, but there was a faster release under acidic conditions.\textsuperscript{145} Their results concluded that drug release was due to surface erosion of the hydrogel at the different temperatures and the surfactant active properties can allow for them to be utilized as smart materials for drug delivery.
### 1.4.2 pH RESPONSIVE GELATORS

Another interesting stimulus that has been investigated for low molecular weight gelators is pH. Generally, the molecules are engineered to have ionizable groups that can donate or accept ions/protons and so changes in the pH induces a response within the gel. This response usually happens when the pH gets higher than the pKa of the gel. The sol-gel transitions for many soft materials have been reported at different pH values and a few examples will be discussed in this section. Figure 24 depicts the structure of a glycolipid that formed different assemblies based on the pH. The researchers utilized small angle X-ray scattering (SAXS) to gain insight into the morphology of the self-assembled glycolipid that was dissolved in water at different pH values. They found that below pH 4, most of the COO− ions turned to COOH and lamellar structures were formed, whilst at basic pH the micelles acquired an ellipsoidal shape that turned into elongated cylinders which were further fused into large discs between pH 6.5 and 7.5. They also studied another similar molecule with a sophorose moiety instead of the glucose headgroup and the results

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Figure 23. Ionogels made from cetylpyridinium salicylate and its response to temperature changes. Adapted from ref 148 under the creative commons license. Copyright (2020) Wiley-VCH Verlag GmbH & Co.
also confirmed morphological changes at various pH conditions.\textsuperscript{146} Their overall results presented a pH dependent system that could be utilized as a model for membrane morphologies which can help to study future complicated systems.

\begin{center}
\includegraphics[width=\textwidth]{figure24.png}
\end{center}

**Figure 24.** Structure and self-assembly of a pH responsive glycolipid.\textsuperscript{146} Adapted with permission from ref 145. Copyright (2016) American Chemical Society.

Another article highlighted an amphiphilic peptide-based hydrogelator denoted as PEP-1 in figure 25, that formed a spontaneous hydrogel in phosphate buffered saline at a MGC of 1.5 wt\%\textsuperscript{.147} The gel had high stability and exhibited a gel-sol transition at 84 °C, in fact pH was demonstrated to greatly impact the self-assembly of the gelator.\textsuperscript{147} The hydrogel, degraded in the presence of an
acidic or basic environment, due to the presence of the many acidic and amine groups that are in its molecular structure. The studies revealed that the disassembly of the fibrous network was caused by the destruction of the β-sheet structure at both pH conditions. At a neutral pH of 7.4, the researchers concluded that favorable electrostatic interactions between the Asp− and Lys+ residues allow for self-assembly within the molecule but in an acidic pH, protonated Asp and Lys+ are repelling each other and the same goes for the Asp− residues at a basic pH. Further examinations proved that the gel was able to release a dye at a faster rate in an acidic medium and was in fact biocompatible, this shows it may have future applications as a biomaterial.

**Figure 25.** A peptide-based amphiphilic gelator and its response to varying pH conditions. Adapted with permission from ref 146. Copyright (2019) American Chemical Society.
1.4.3 ENZYME RESPONSIVE GELATORS

Enzymes have also been utilized for triggering or disrupting gelation. They have been defined as biological catalysts that work best in a physiological environment to form new bonds or bring about modifications in different molecules. The use of enzymes as stimuli is very advantageous especially for biomedical applications, they occur naturally in the body and certain imbalances or overexpression at disease sites can be exploited to generate material response in situ. In addition to that, they are catalytically efficient due to their selectivity and specificity for substrates. Enzymes also function on their own because their properties are endogenous. There have been a tremendous amount of enzymes reported in the literature as stimuli, however, the most common ones are kinases, endonucleases, proteases and phosphatases. Enzymatic action can bring about self-assembly or disassembly within a material. Consequently, when designing enzyme responsive materials, several features must be considered; the material must have the moiety that is sensitive to the enzyme and the action of the enzyme must be translated throughout the material which will then induce changes in the material’s properties. In this section a few examples of enzyme responsive materials will be discussed briefly.

A glycopeptide shown in figure 26 was able to form a gel after being cleaved by alkaline phosphatase (ALP). The molecule contains a naphthyl group and a dipeptide unit Phe-Phe that allowed for its inherent self-assembly via \( \pi-\pi \) interactions. The molecule also has a D-glucosamine headgroup which aids in cellular attachment and cell growth as well another peptide unit (Asp-Tyr(H\(_2\)PO\(_3\))) bearing a phosphate group for enzymatic catalysis by ALP. Gel formation was reported to occur at a concentration of 0.6 wt % and a pH of 7.4 in water after treatment with ALP at a concentration of 10 units/mL. The morphology of the gel was fibrous with a porous 3D
structure and the gel had suitable rheological properties for tissue engineering. The researchers utilized human umbilical vein endothelial cells (HUVECs) to test the gel as a medium for cell growth. In addition to that, the gel was able to entrap a growth factor deferoxamine (DFO), which was injected in the dorsal side of mice and the gel remained relatively stable overtime and assist with vasculogenesis in mice as depicted in figure 26.\textsuperscript{149}
Enzyme responsive materials such as those in figure 27 have also been engineered to respond to β-Galactosidase (β-gal). Two glyconucleo-bolaamphiphilic molecules (72-73) were generated by using click chemistry to attach lactose to a nucleotide.\footnote{150} Compound 72 was not able to congeal phosphate buffered saline (PBS) but a viscous solution was seen at a concentration of 5\% (wt/vol) and compound 73 formed a hydrogel at 2\% (wt/vol).\footnote{150} However, both compounds were able to form hydrogels at varying concentrations after been cleaved with β-gal to give compounds 74-75. Their results demonstrated that the molecular assemblies that formed after enzymatic catalysis were in fact stronger than the gelator precursors.\footnote{150} The \textit{in situ} formation of the gel networks presented in this paper can be utilized in many therapeutic methods.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure27.png}
\caption{Structures of glyconucleo-bolaamphiphiles that are responsive to β-Galactosidase (β-gal).\footnote{150}}
\end{figure}
1.4.4 PHOTO-RESPONSIVE GELATORS

Self-assembled networks can also respond to light as a stimulus. There have been many reports of these gelators that span from polymers to small molecules. Due to the fact that light is non-invasive, it is used widely as a stimuli to develop photo responsive systems. There are many ways in which light responsive gelators behave, but some of the most common responses are explained in figure 28. There can be disruption of the gel network, modification in the gel morphology and even the formation of a gel after being exposed to light. In order for a gelator molecule to respond to light, a chromophore must be present in its structure, the chromophore is generally made up of a conjugated system which can bring about π-π stacking and other interactions for gelation to occur. Some of the common chromophores that have been utilized are azobenzenes, stilbenes, alkenes, coumarins and anthracenes. The reactions that bring about these molecular responses to light include, isomerization, bond cleavage, dimerization and bond formation. Herein, a few examples of photo responsive gelators in the literature will be discussed.
A multi-stimuli responsive, fluorescent gelator was synthesized from a polyaryl dendron core with anthracene attached through an acyl hydrazone bond. The best performing molecule from the series is shown in figure 29. It does not fluoresce as a solution, but upon forming a gel and after irradiating with UV light the emission intensity of the bright green luminescence improves. The gel was also able to detect low concentrations of fluoride and the authors concluded that gel induced enhanced emission characteristics can be applied to the creation of light emitting devices and transistors.
Several amphiphilic disaccharides with azobenzene moieties were synthesized and studied for their gelation properties and response to light. The representative molecular structures that were generated are depicted in figure 12 and a few of them were able to form gels, with compounds 38a and 38c being the best performing in the series. The azobenzene component was an instrumental part of the self-assembly mechanism which was the formation of H-type aggregates through \( \pi-\pi \) stacking of the aromatic rings.\(^{24} \) The gels underwent the gel-sol transition after being irradiated with UV light at a wavelength of 365 nm which the authors attributed to the \textit{trans-cis} photoisomerization in the azobenzene that breaks down aggregation within the gel.\(^{24} \) However, after approximately 12 h, the gels were able to reform under weak visible light. The gels were also able to bind lectins and showed their potential to be utilized as a medium for cell-culture.

\section*{1.5 APPLICATIONS OF LMWGS}

Gels have very important applications that span many fields, especially at the interface of material science, chemistry, engineering and biochemistry. Over the years, LMWGs have been studied for
applications such as in optical devices, conducting cloths, lectin binding, self-healing, removal of metal ions, for the absorption of carbon dioxide, catalysis and many others. In this segment, a few applications for gelators will be discussed. These include drug delivery, enzyme immobilization, tissue engineering, environmental remediation, and wound healing.

1.5.1 DRUG DELIVERY

Gelators in general are being studied heavily for applications in drug delivery and other biomedical applications. This is because many drugs have to be administered repeatedly in order to have maximum efficacy and many have poor solubility which leads to low bioavailability. With this, investigational studies looking at other alternative ways to bring drugs to their site of action are rather significant in the field. Systems such as micelles, liposomes and gels from polymers or small molecules have been examined for this purpose. However, regardless of the approach used; there are three main ways in which drug delivery is achieved. A prodrug can be generated by covalently attaching the drug to another self-assembling moiety that can slowly degrade after cleavage in the presence of an enzyme. Another option is that an amphiphilic drug could be covalently attached to a functionalized linker that is responsive to an enzyme and after enzymatic activity at the linker, the drug self-assembles. In addition to that, the drug can also be entrapped within the gel network and then slowly released by way of diffusion or from the breaking down of the gel matrix. Many examples of these systems have been studied for drug delivery and several stimuli responsive gels have also been investigated for the latter application. Even though several organogels have been examined for drug delivery due to their interesting properties, their biggest drawback is safety because of the solvent systems used for gel formation. More recently, hydrogels have gained increased attention for usage in drug delivery because toxicity is much
lower and the drug is protected while encapsulated. A few examples of various systems for drug delivery are discussed next.

Raymond et al. recently discovered several cationic hydrogels developed from N-Fluorenylmethoxycarbonyl phenylalanine (Fmoc-Phe). The molecules were derivatized with diaminopropane (DAP) at the end containing the carboxylic acid and it was confirmed that the DAP moiety enhanced the water solubility of the compounds at a range of pH values. The authors also mentioned that fluorination of the aromatic side chain substantially improves the potential for self-assembly with the best performing molecule depicted in figure 30. The aforementioned compound was able to form a gel with a fibrous network at 30mM in water and concentrated sodium chloride making it a final concentration of 33.7 mM. The gel was stable at physiological conditions which demonstrated potential to be utilized in drug delivery. The researchers were able to encapsulate diclofenac within the gel matrix and examine its release both in vitro and in vivo. The in vitro studies demonstrated a slow and steady release of the drug over a period of days, based on the mechanical stability of the gel it was also utilized in vivo. The studies were done with a model of mice where pain was induced in the ankle joint of the hind leg by dispensing complete Freund’s adjuvant (CFA). Based on their results, the diclofenac was slowly released over a period of two weeks and was able to relieve pain the mice. The finding illustrates that salt-based gelators have immense potential to be utilized in drug delivery with high stability.
An interesting gelator derived from guanosine was also reported for its use in drug delivery. The authors employed the ability of guanosine to coordinate into cyclic tetramers also referred to as G-quartets in the presence of metal ions. These highly ordered gel systems have interesting properties that allow for their utilization in different applications. The guanosine monophosphate molecule was able to form a hydrogel due to its assembly into a G-quadruplex structure that was cross-linked through Ca$^{2+}$ and Fe$^{3+}$ ions as seen in figure 31. The calcium ions linked the sugar moieties and was found to increase the mechanical strength of the network, whilst the iron ions formed the complex by interacting with the phosphate groups. The hydrogel was capable of entrapping doxorubicin at a high loading capacity, the drug was also slowly released from the gel over a period of several days at a pH of 4 and 5.5, but at pH 7.4, a much slower release was seen due to better
stability at that pH.\textsuperscript{157} The overall results demonstrated that the, low–cost biocompatible hydrogel has great potential for utilization in biomedical applications.

Figure 31. A guanosine quadruplex hydrogel system and its usage in the delivery of doxorubicin (Dox) under acidic conditions.\textsuperscript{157} Adapted with permission from ref 156. Copyright (2019) American Chemical Society

A glycosylated nucleoside–based bola–amphiphilic gelator bearing disulfide bonds, was also produced for the sustained release of biomolecules. The disulfide group was introduced into the gelator architecture as a linker between the two amphiphiles. The researchers hypothesized that the presence of the disulfide bond would enable the release of thiol containing molecules through redox reactions.\textsuperscript{158} The compound in figure 32 formed a stable hydrogel which had thixotropic properties based on the rheological studies; this also enables the gel to have the mechanical characteristics for administering in vivo via injection.\textsuperscript{158} Their investigations confirmed that the gel was degraded in the presence of dithioerythritol (DTT) and other redox molecules due to thiol-
disulfide exchange reactions that disrupt the disulfide bonds. Further experiments also showed that
the gel was biocompatible and that it had potential in future applications where this sulfide delivery
system could be advantageous.

![Figure 32](image)

**Figure 32.** A glycosylated nucleoside-based bola-amphiphilic (GNBA) gelator.\(^{158}\)

1.5.2 **ENZYME IMMOBILIZATION**

Enzymes are biological catalysts that speed up biochemical reactions in our bodies or regular
chemical reactions with high specificity and efficiency.\(^{159, 160}\) They also help to make several
processes more environmentally safe. Enzymes are utilized heavily in industries to carry out
reactions and create new products.\(^{161}\) However, there are still challenges with using enzymes on
an industrial scale, they often cannot be recycled and are not very stable throughout the
reactions.\(^{159}\) Excitingly, researchers have come up with new strategies to combat this and the
solution is enzyme immobilization. Enzyme immobilization is a process whereby biological
catalysts are restrained to a specific location via different methods. The main ways in which
enzyme immobilization is achieved are through entrapment, covalent bonding, and adsorption.\(^{160, 162-164}\)

A schematic diagram representing these methods, is shown in figure 33. The most common
method that has been exploited for enzyme immobilization is entrapment because it allows for the
enzyme to remain within a gel matrix and does not require binding to the active sites as with covalent bonding.\textsuperscript{159}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure33.png}
\caption{Methods for enzyme immobilization (adsorption, entrapment, and covalent bonding).\textsuperscript{159} Adapted from ref 158, under the creative commons license. Copyright (2019) MDPI.}
\end{figure}

A very recent example of enzyme entrapment within a supramolecular gel matrix was reported by Falcone et al., where synthesized amphiphilic myristyl-phenylalanine gels were used to immobilized $\alpha$-amylase and horseradish peroxidase (HRP). The gel photos and molecular structures of the two derivatives can be seen in figure 34. They were both able to form stable gels in a phosphate buffer solution at pH 7, with long fibers making up the bulk of the gel matrix.\textsuperscript{159}

Both hydrogels were capable of entrapping horseradish peroxidase and $\alpha$-amylase; the enzymes retained their catalytic activity and were able to carry out biochemical reactions while immobilized.\textsuperscript{159} The $\alpha$-amylase was still able to break down starch to maltose which was detected using a colorimetric assay and horseradish peroxidase was able to break down pyrogallol in the presence of hydrogen peroxide to purpurogallin.\textsuperscript{159} Both reactions took place in solutions on top of the gels, therefore it was important for the researchers to investigate if the enzyme was leaching out of the gel and catalyzing the reactions. Based on their studies there was minimal leaching, and
the activity of the leached enzyme was very much lower than the activity of the entrapped enzyme. The enzymes remained stable and functional for a long period of time whilst acting on new substrate solutions. These results demonstrated that the gels can be utilized for immobilizing enzymes to carry out more environmentally friendly reactions on an industrial scale.

**Figure 34.** Gel photos and chemical structures of the, a) Gel formed by the L-Phenylalanine derivative 77a; b) Gel formed by the D-Phenylalanine derivative 77b. Adapted from ref 158, under the creative commons license. Copyright (2019) MDPI.

### 1.5.3 TISSUE ENGINEERING

Low molecular weight gelators have immense potential to be utilized as soft materials in biomedical sciences not only because they are biocompatible, but also the gel matrix can be made to imitate cellular environments. Tissue engineering is also known as regenerative medicine and
constitutes methods which allow for the regeneration of cells or tissues outside of the body.\textsuperscript{165} This area of biomedical sciences is quite significant and requires interdisciplinary research as the overall goal is to combat organ failure and several diseases that result from tissue damage.\textsuperscript{166, 167} In order for a biomaterial to be successfully applied in regenerative medicine, it must have several design features. Biocompatibility is very important for the gel to be non-toxic, the gels must also be biodegradable and the products generated during degradation must be non-toxic as well.\textsuperscript{166} Additionally, the gel matrix must be stable and strong with the innate chemistry for cell attachment, proliferation and differentiation; it should also possess a porous architecture that provides fundamental support for the cells and the passage of wastes and nutrients. Though the field has been dominated by polymeric gels,\textsuperscript{168-170} low molecular weight gelators have also been studied and will be highlighted in this section.

An excellent example of a carbohydrate-based gelator for tissue engineering was generated from N-heptyl-galactonamide and a few structures are shown in figure 35. All three molecules formed biocompatible hydrogels with the best performing being 78b at a MGC of 0.45 wt %.\textsuperscript{65} The latter gel was investigated as a medium for cell growth and the studies revealed that adult human neuronal stem cells were able to make neurosphere-like structures whilst growing deep (~200 μm) in the gel matrix. They also observed that the cells differentiated into neuronal and glial cells that developed a fully intertwined neuronal network.\textsuperscript{65} This gelator molecule that can be acquired at the gram scale from a facile one-step synthetic method, certainly displayed the ideal characteristics needed for its utilization in tissue engineering.
1.5.4 ENVIRONMENTAL REMEDIATION

Wastewater treatment is a constant and growing concern today, this is because harmful chemicals and oils get into our water reserves almost every day. Previously, the materials that were exploited for cleaning up pollutants posed detrimental risks as many were more toxic than the pollutants themselves. Subsequently, the latter situation caused researchers to investigate new approaches for solving this problem and many have studied soft materials like gels because many of them are nontoxic, biodegradable and can be easily modified to give new molecules. In order for the gels to be successful in removing chemicals and other waste, they must be able to establish strong interactions with the particular pollutants; so designing gelators for this purpose remains a challenge. Nonetheless, there have been reports of several supramolecular gelators that have shown excellent potential for different aspects of environmental remediation and a few examples will be discussed here.

Interestingly, several carbohydrate-based gelators have been reported for dye removal, oil spill clean-up, and the removal of metal ions. Scheme 1 below shows the synthetic route for generating gelator 81 from N-acetyl-d-glucosamine. Compound 81 was able to form gels in a wide variety of organic solvents such as mesitylene, toluene and benzene at concentrations as low as...
The gelator was also able to congeal petrol and diesel so they tested its phase selective gelation properties; a solution of the gelator in tetrahydrofuran was able to form strong gels when placed in a mixture of water and petrol or diesel. In fact the gels could be removed from the solutions with a spatula and the fuel components were recovered by way of distillation. The gels were quite versatile in their utility as the toluene gel of compound 81 was able to absorb approximately 96% of rhodamine B base from a solution that was placed on top of it. Furthermore, compound 81 not only form gels in organic solvents but hydrogels were also reported. Overall, their results demonstrated that this gelator was multifaceted and holds great promise for applications in environmental remediation.

An imidazolium-based gelator was also developed for dye removal and the research surrounding it is summarized in figure 36. The gelator was able to form a gel at 20 wt % in a mixed solvent system of DMSO and water at a ratio of 40/60 (wt/wt) with very high stability. Figure 36 shows that the mechanism of self-assembly involves the π-π stacking of the imidazolium rings, hydrogen bonding amongst the carboxylic groups and hydrophobic interactions between the alkyl chains to generate the platelet assemblies that were apparent under the microscope. The DMSO:water gel
was also able to selectively remove anionic dyes from solution. The researchers tested both cationic (rhodamine 6G, methylene blue) and anionic dyes (eosin Y, methyl orange). They found that the gels were able to successfully remove methyl orange and eosin Y from aqueous solutions. Moreover, the gel could be recycled and was able to selectively remove eosin Y from a mixture of methylene blue and eosin Y. This confirms that it is particularly useful for the adsorption of anionic dyes due to the favorable interactions between the dye molecules and the gels.\textsuperscript{177}

**Figure 36.** Self-assembling mechanism of an imidazolium-based surfactant and its usage in dye absorption.\textsuperscript{177} Adapted with permission from ref 176. Copyright (2015) American Chemical Society.
1.5.5 ANTIBACTERIAL AGENTS

Another interesting application of gelators is their use as antibacterial agents, this application is often coupled with wound healing. Most of the gelators that have been reported as agents for wound healing also have high stability and thixotropic properties that allow for them to be applied as wound dressings. The cytidine derivative shown in figure 37 was mixed with boronic acid and silver acetate at different ratios to give hydrogels with innate antibacterial properties. The gel was thermo-reversible with self-healing properties and was able to recover from damage due to mechanical stress. The hydrogel was not very effective against gram-positive bacteria such as *Streptococcus pneumoniae* and *Staphylococcus aureus*. On the other hand, the minimum inhibitory concentrations of the gels required to hinder bacterial growth were much lower for the gram-negative strains such as, a multidrug resistant strain of *Morganella morganii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli*. The researchers also investigated the cytotoxic effects of the hydrogel on human normal kidney epithelial (NKE) cells, they found that it was non-toxic even though silver acetate on its own is in fact toxic. Consequently, discoloration of the tissues was not observed at the application site where the silver acetate containing hydrogel was placed. This led the authors to believe that this method is more beneficial than using silver nitrate in antibacterial gels.
Figure 37. Multicomponent gel from cytidine and phenylboronic acid with antibacterial properties.\textsuperscript{178} Adapted with permission from ref 177. Copyright (2019) American Chemical Society.

Other sugar-based molecules such as the monosaccharides in figure 38, have also shown promising results at breaking up biofilms. They were efficient gelators for oils and more hydrophobic solvents, but surprisingly formed foam in water; the foam remained stable at room temperature for around 6 h.\textsuperscript{179} The solutions of both gelators were allowed to interact with biofilms from different bacterial strains. The compound without the long aliphatic chain in figure 38 was able to disrupt biofilms formed by gram positive \textit{Staphylococcus aureus} and \textit{Listeria monocytogenes}.\textsuperscript{179} The other gelator, was more potent against the bio-films from uropathogenic \textit{Escherichia coli} and \textit{Salmonella enterica Typhimurium}.\textsuperscript{179} Overall, these results demonstrate the potential of these supramolecular materials to be applied as cleaning agents, both as a solution or a gel.
Figure 38. Sugar-based molecules for disassembling biofilms. Adapted with permission from ref 178. Copyright (2017) American Chemical Society.
CHAPTER 2

SYNTHESIS AND CHARACTERIZATION OF N-ACETYL-D-GLUCOSAMINE DERIVED GLYCOLIPIDS AS FUNCTIONAL GELATORS

PREFACE
This chapter is adapted from the following publication:


2.1 INTRODUCTION

Low molecular weight gelators (LMWGs) are useful compounds for the preparation of soft gel-like materials. The resulting gels are reversible and are called physical gels or supramolecular gels, which are composed of crosslinked networks with the solvents as the main component of the gels.\textsuperscript{180-184} The interactions that govern the intricate supramolecular network formed by these gelators are non-covalent interactions. These include hydrogen bonding, van der Waals forces, π-π stacking, CH-π interactions, electrostatic interactions, as well as hydrophobic interactions.\textsuperscript{6, 44, 185, 186} Many different classes of natural compounds have been reported as molecular gelators, some of which include oligopeptides, carbohydrate derivatives, and cholesterol derivatives. Compounds containing functional groups such as urea, urethane, amide, aromatic and long chain alkyl groups are found to be effective organogelators and hydrogelators.\textsuperscript{187, 188} They have shown applications in a variety of research fields including environmental applications, biomedical research and catalysts for synthesis.\textsuperscript{189-196} Among the different classes of gelators, we are more interested in using sugars as the building blocks due to their biocompatibility and biodegradability.
Carbohydrate derivatives have been utilized extensively as scaffolds for biomaterials with different functions. One important facet of carbohydrates is the presence of multiple functional groups that can form hydrogen bonds, which are necessary for supramolecular systems and self-assembly.\textsuperscript{101, 197, 198} The versatile hydrogels and organogels obtained from carbohydrate derivatives have shown remarkable applications in a variety of research fields.\textsuperscript{69, 198-200} These include but are not limited to biomedical applications such as drug delivery, tissue engineering, and enzyme immobilization.\textsuperscript{200-202} Several LMWGs and other supramolecular gelators have shown applications in environmental chemistry for pollutant removal, phase selective gelation and as methods for oil spill clean-up.\textsuperscript{203-210} Compounds containing functional groups that are responsive towards different stimuli including acids and bases or enzymes are useful new materials with stimuli-responsive properties.\textsuperscript{211} For instance, phosphatase responsive gelators have shown remarkable applications as anticancer agents with a new mode of action, physical gelation.\textsuperscript{212, 213}

We have been working on the selective functionalization of sugar templates that are suitable for gelation and molecular self-assemblies and obtained several different classes of sugar-based LMWGs.\textsuperscript{80, 82, 83, 88, 89, 97, 214} Most of the gelators were able to form physical gels composing of up to ~2 wt \% gelator and ~98\% solvents. The structures of a few examples are shown in figure 39. Certain alkyl derivatives of the 2-\textit{O}-ester from the glucose compound 1, were gelators for numerous solvents. The amide derivatives from compound 2 were more efficient gelators with a wide range of functional groups; many of the compounds formed gels in mixtures of DMSO and water or ethanol and water, and a few formed hydrogels.\textsuperscript{80, 82, 88, 214} Recently we reported a hybrid system 3,\textsuperscript{97} in which a triazole functional group was introduced to the amide 2; these compounds were found to be extremely effective gelators and more compounds formed hydrogels in
comparison to the simple amide derivatives 2. Many gelators have been produced by functionalizing the different hydroxyl groups in N-acetyl-D-glucosamine and so to investigate the effect of other functional groups on gelation, we incorporated amide and ester functionalities in the gelators. The hybrid model 4 combines the functional groups mentioned earlier and it should lead to effective LMWGs since the modification will not alter the molecular assemblies much, while adding an additional hydrogen bonding acceptor to the molecules. Additionally, the ester functional group is responsive to bases and could be cleaved either under basic conditions or lipase enzymatic cleavage. Consequently, compounds with the general structure 4 could lead to a new class of functional and stimuli-responsive gelators.

![Chemical structures of different sugar-based gelators and the structure of a novel class of hybrid amide ester gelator system 4.](image)

**Figure 39.** Chemical structures of different sugar-based gelators and the structure of a novel class of hybrid amide ester gelator system 4.

### 2.2 RESULTS AND DISCUSSION

The synthesis of the series of esters is shown in scheme 2. Compound 5 which is the starting material, was prepared from N-acetyl-D-glucosamine.\(^{88, 97}\) It was then treated with bromo-acetyl
chloride or bromo-acetyl bromide to afford the headgroup 6, then the bromo group was displaced by different carboxylates by way of an S\textsubscript{N}2 reaction to obtain a series of esters 4. To probe the structural impact towards gelation properties, a series of different alkyl and aryl carboxylate esters were synthesized and characterized. Their gelation properties were determined, and the results are shown in table 1. The MGCs were included for the gels formed by these compounds.

Scheme 2. Synthesis of the hybrid amide and ester derivatives.
2.2.1 GELATION PROPERTIES OF THE MOLECULES

All fifteen compounds formed gels in several of the tested solvents, the only compound that didn’t perform as well as the others was the t-butyl ester. The branched ester derivative only formed gels in ethylene glycol and glycerol at higher concentrations. The short chain pentyl ester 8 was the most versatile gelator, forming gels in ten out of the eleven tested solvents. It also formed a hydrogel at 0.14 wt %. The longer alkyl derivative heptynoate 9, formed gels in eight of the tested solvents, but typically required higher concentrations for gelation in comparison to the pentanoate 8. Compound 9 formed a hydrogel at 0.29 wt %. The cyclohexyl ester 10 was also an efficient gelator for toluene, isopropanol, and aqueous mixtures of ethanol or DMSO. For the linear aliphatic derivatives, increasing the chain length in compounds 11, 12 and 13 to fifteen, sixteen and nineteen carbons increased the hydrophobicity of the compounds, they only formed gels in organic solvents but not in water and the aqueous solutions. The longest chain ester 13 was the most effective gelator for toluene, forming a gel at 3.3 mg/mL. All aromatic ester derivatives were gelators for at least four of the tested solvents, among these the 2-furan ester 14, benzoate 15, 3-chlorobenzoate 16 and 4-methoxybenzoate 17 were the most versatile gelators, forming gels in eight or nine of the tested solvents. They were effective for aqueous mixtures of DMSO or ethanol, with the chloro or methoxy substituted aryl derivatives being the most efficient in DMSO and water mixtures. The 4-nitrobenzoate derivative 18 performed well too, however the bulkier 4-bromobenzoate 19 was not as effective as the rest. The addition of another aromatic ring as in the 1- or 2-naphthalene derivatives 20 and 21 diminished gelation slightly. It is interesting to observe that the stereoisomers gave different gelation properties, with the 2-naphthylacetate 21 being more proficient in comparison to the 1-naphthylacetate 20. Most of the gels were opaque or translucent with a few being transparent. A few representative gel photos are shown in figure 40.
Table 1. The gelation test results of compounds 7-21.

<table>
<thead>
<tr>
<th>Cpd. #</th>
<th>Tol</th>
<th>i-PrO</th>
<th>EtOH</th>
<th>EG</th>
<th>Glycerol</th>
<th>TEG</th>
<th>EtOH :H$_2$O (1:2)</th>
<th>EtOH :H$_2$O (1:1)</th>
<th>DMSO :H$_2$O (1:2)</th>
<th>DMSO :H$_2$O (1:1)</th>
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<td>7</td>
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<td>P</td>
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<td>G20.0</td>
<td>S</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>I</td>
</tr>
<tr>
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<td>G6.7o</td>
<td>G10.0</td>
<td>G10.0c</td>
<td>G2.5c</td>
<td>S</td>
<td>G2.9t</td>
<td>G10.0o</td>
<td>G2.5t</td>
<td>G5.0c</td>
<td>G1.4o</td>
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<tr>
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<td>G20.0o</td>
<td>S</td>
<td>S</td>
<td>G5.0c</td>
<td>S</td>
<td>G6.7o</td>
<td>G10.0o</td>
<td>G10.0o</td>
<td>G10.0o</td>
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</tr>
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<td>G6.7o</td>
<td>S</td>
<td>G10.0c</td>
<td>G10.0</td>
<td>S</td>
<td>G5.0o</td>
<td>G5.0o</td>
<td>G5.0o</td>
<td>G4.0t</td>
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<td>P</td>
<td>G4.0o</td>
<td>G10.0c</td>
<td>G4.0o</td>
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<td>I</td>
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<td>I</td>
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<td>G10.0c</td>
<td>I</td>
<td>P</td>
<td>I</td>
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<td>I</td>
</tr>
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<td>G6.7o</td>
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<td>G20.0c</td>
<td>G5.0t</td>
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<td>G10.0r</td>
<td>G20.0c</td>
<td>G20.0o</td>
<td>G6.7o</td>
<td>G5.0o</td>
<td>G5.0o</td>
<td>I</td>
<td></td>
</tr>
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<td>G20.0o</td>
<td>G5.0t</td>
<td>G3.3t</td>
<td>G20.0c</td>
<td>I</td>
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<td>G6.7o</td>
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<td>G20.0t</td>
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<td>G1.4t</td>
<td>G1.4t</td>
<td>I</td>
</tr>
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<td>G10.0c</td>
<td>G20.0c</td>
<td>I</td>
<td>G1.3t</td>
<td>G1.3o</td>
<td>G1.3t</td>
<td>I</td>
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<td>G4.0c</td>
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<td>P</td>
<td>P</td>
<td>G2.2t</td>
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</tr>
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<td>G10.0o</td>
<td>G20.0o</td>
<td>S</td>
<td>S</td>
<td>I</td>
<td>G4.0o</td>
<td>I</td>
<td>I</td>
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</tr>
<tr>
<td>20</td>
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<td>P</td>
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<td>G20.0o</td>
<td>G6.7o</td>
<td>S</td>
<td>I</td>
<td>P</td>
<td>G5.0o</td>
<td>G20.0o</td>
<td>I</td>
</tr>
<tr>
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<td>G20.0o</td>
<td>P</td>
<td>G10.0r</td>
<td>G5.0r</td>
<td>S</td>
<td>I</td>
<td>G20.0o</td>
<td>G5.0o</td>
<td>G5.0o</td>
<td>I</td>
</tr>
</tbody>
</table>

All compounds were tested starting from 20 mg/mL. G, stable gel at room temperature, the numbers are the minimum gelation concentrations (MGCs) in mg/mL; P, precipitate; S, soluble; I, insoluble; PG, partial gel; T, translucent; C, clear; O, opaque. Hex-hexane, Tol-toluene, EG-ethyleneglycol, TEG- triethylene glycol. All tested compounds were soluble in THF, and most were insoluble in hexane.
Figure 40. Gel photos of compounds 9, 10, 16 and 18. a) A clear gel of compound 9 in glycerol at 5.0 mg/mL; b) an opaque gel of compound 10 in DMSO:H₂O (v/v 1:2) at 5.0 mg/mL; c) a translucent gel of compound 16 in DMSO:H₂O (v/v 1:2) at 1.4 mg/mL; d) a translucent gel of compound 18 in DMSO:H₂O (v/v 1:2) at 2.2 mg/mL.

The gels were characterized using optical microscopy to obtain molecular assembly information. A few selected samples are shown in figure 41. The series of compounds formed effective gels in many solvents, typically the gels exhibited fibrous morphologies. The gel of compound 9 in EtOH:H₂O (v/v 1:2) exhibited fibrous aggregates (fig. 41a). The gel of compound 10 in EtOH:H₂O (v/v 1:2) showed long fibrous networks with densely aligned birefringent fibers (fig 41b). The gels in DMSO:H₂O (v/v 1:2) also showed similar fibrous features (fig. 41c-e). The furan derivative 14 formed long uniform fibers with lengths over 100 µm (fig. 41c) and the gel of compound 16 showed similar birefringent long fibrous networks with lengths over 200 µm (fig. 41d). The gel of compound 20 showed shorter fibers with less than 100 µm in length (fig. 41e). Figure 41f shows the morphology of the wet gel formed by compound 18 with toluidine blue (TBO), clusters of fibers were arranged around fan shaped assemblies.
Figure 41. Optical micrographs of a few representative ester gels under brightfield. a) compound 9 in EtOH:H$_2$O (v/v 1:2) at 6.7 mg/mL; b) compound 10 in EtOH:H$_2$O (v/v 1:2) at 4.0 mg/mL; c) compound 14 in DMSO:H$_2$O (v/v 1:2) at 5.0 mg/mL; d) compound 16 in DMSO:H$_2$O (v/v 1:2) at 1.4 mg/mL; e) compound 20 in DMSO:H$_2$O (v/v 1:2) at 5.0 mg/mL, f) compound 18 in DMSO:H$_2$O (v/v 1:8) at 2.25 mg/mL (for the gel only, gel volume was 2 mL) and toluidine blue dye (TBO) at 0.031 mg/mL. The scale bar is 20 µm for all images.
To further characterize the surface morphological properties, atomic force microscopy (AFM) studies were carried out for several gelators. AFM is a higher resolution type of microscopy that is utilized to study and examine surfaces to yield detailed information at the nanoscale level. It is also utilized for analyzing gel morphology along with SEM. Figure 42 shows the AFM images of the hydrogel formed by compound 9, which exhibited long, continuous fibrous assemblies throughout the matrix. The DMSO:H₂O (v/v 1:2) gel formed by compound 16 showed shorter fibrous aggregates depicted in figure 43 and they were not as continuous as those seen for compound 9. The gel formed by compound 18 in DMSO:H₂O (v/v 1:8) in the presence of toluidine blue, showed twisted ribbon like morphologies as illustrated in figure 44. Altogether, the microstructures that were observed for the representative gels, showed the fibrous morphology that is typically seen for most gel matrices. The AFM images illustrated more detailed structure information of the assemblies in comparison to the optical micrographs.
Figure 42. AFM images of the hydrogel formed by compound 9 at 2.9 mg/mL. The top image is the height data map, and the bottom is the phase image for the amplitude scan. The images were acquired using tapping mode.
**Figure 43.** AFM images for the gel formed by compound 16 in DMSO:H_2O (v/v 1:2) at 1.4 mg/mL. The top image is the height data map, and the bottom is the phase image for the amplitude scan. The images were acquired using tapping mode.
Figure 44. AFM images for the gel formed by compound 18 in DMSO:H$_2$O (v/v 1:8, 2.3 mg/mL) and toluidine blue (0.031 mg/mL). The top image is the height data map, and the bottom is the phase image for the amplitude scan. The images were acquired using tapping mode.
2.2.2 MECHANICAL PROPERTIES AND GEL STABILITY

In order to analyze the mechanical properties and stability of the gels, several rheological experiments were performed on the hydrogels and organogels formed by the gelators. The results are illustrated in figure 45. The amplitude sweep experiments were carried out first to obtain the linear viscoelastic range that would be needed to carry out the frequency sweep. As shown in figure 45, the storage modulus \( G' \) was greater than the loss modulus \( G'' \) for all the gels that were analyzed; which validated that the gels were stable with viscoelastic properties. The hydrogel formed by compound 8 has larger \( G' \) (over 100 kPa) values than the gel formed by compound 9, which means that the hydrogel of 8 is relatively stronger when both gelators are at their MGCs. The rheological properties of the DMSO:H\(_2\)O (v/v 1:2) gels for compounds 10, 16, 17, 18, and 20 are also included in figure 45. Among these, the gel of cyclohexyl ester 10 exhibited the highest \( G' \) (over 100 kPa) values, followed by that of compound 18. The latter compounds were the most stable gels based on the rheological experiments.
Figure 45. Rheological properties of the hydrogels of compound 8 (H₂O, 1.4 mg/mL), compound 9 (H₂O, 2.9 mg/mL) and the gels in DMSO/H₂O (v/v 1:2) for compounds 10, 16, 17, 18, and 20. The concentrations of the gelators are: compound 10 (5.0 mg/mL), compound 16 (1.4 mg/mL), compound 17 (1.3 mg/mL), compound 18 (2.2 mg/mL), and compound 20 (5.0 mg/mL).

To further analyze the gels’ thermal stability, the melting points of a few representative gels in DMSO:H₂O (v/v 1:2) were measured and these are listed in table 2. The median melting temperature can represent the relative thermal stability of these gels. The melting temperatures of the gels seem to be structure dependent, with the aromatic esters (16 and 20) having higher melting points than the aliphatic esters (8 and 10). The melting behavior of the gels were affected by the strength of the interactions within the intricate network whereby the gels with stronger intermolecular forces should have a higher melting point than others.
Table 2. Melting points of a few representative gels in DMSO:H₂O (v/v 1:2)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Concentration (mg/mL)</th>
<th>Molar concentration (mM)</th>
<th>T₁ °C</th>
<th>T₂ °C</th>
<th>T₃ °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td></td>
<td>2.5</td>
<td>5.9</td>
<td>34.0</td>
<td>58.0</td>
<td>92.8</td>
</tr>
<tr>
<td>10</td>
<td></td>
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<td>11.1</td>
<td>40.9</td>
<td>54.9</td>
<td>113.9</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>1.4</td>
<td>3.0</td>
<td>57.3</td>
<td>65.5</td>
<td>126.1</td>
</tr>
<tr>
<td>20</td>
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<td>5.0</td>
<td>10.1</td>
<td>60.5</td>
<td>93.0</td>
<td>124.0</td>
</tr>
</tbody>
</table>

T₁ - initial melting temperature, T₂ - temperature at which half of the gel has melted, T₃ - temperature at which the gel finished melting.

2.2.3 DRUG RELEASE STUDIES

For applications in biological systems the hydrogelators or gels with a small amount of DMSO are preferable. Therefore, the gelation properties of compounds 16, 17 and 18 were studied in different proportions of DMSO and water; the results are summarized in table 3. All three gelators formed gels in DMSO:H₂O at 1:1 and 1:2 ratios. Upon serial dilution, compound 18 formed gels in DMSO/H₂O at ratios of 1:3, 1:4, 1:5, 1:6, 1:7, and 1:8. Compound 18 formed a gel at 1:8 volume ratio of DMSO/water at 2.2 mg/mL. The p-methoxy benzoate 17 also formed gel at 12.5% DMSO in water at 2.5 mg/mL; but the 3-chlorobenzoate 16 only formed gels in 25% DMSO in water at 5.0 mg/mL.
Table 3. The final gelation concentrations of a few gels in DMSO/water at different ratios.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structures R</th>
<th>MGC mg/mL</th>
<th>DMSO: H₂O Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Cl</td>
<td>G 5.0O</td>
<td>1:3 25%</td>
</tr>
<tr>
<td>17</td>
<td>O</td>
<td>G 2.5T</td>
<td>1:7 12.5%</td>
</tr>
<tr>
<td>18</td>
<td>O₂N</td>
<td>G 2.2O</td>
<td>1:8 11%</td>
</tr>
</tbody>
</table>

Based on these results, the gels formed by compound 8 in water and compound 17 in DMSO/H₂O (v/v 1:5) were chosen for naproxen entrapping and release studies. These two gelators represented the typical aliphatic and aromatic functional groups for the two types of esters. Compound 8 was an effective hydrogelator, therefore it’s properties for encapsulating drugs or other compounds would be important. Compound 17 represented aromatic ester derivatives and it may interact with aromatic containing compounds more strongly. Naproxen sodium was used as the model drug which represents compounds containing aryl and carboxylate functional groups. A few representative photos of the gel formed by compound 8 with the encapsulated naproxen sodium, are shown in figure 46. The hydrogel was prepared using 2.8 mg of compound 8 and 0.50 mg of naproxen sodium in 2.0 mL of water. Afterwards, 2.0 mL of water (pH ~7) was placed on top of the gel, the UV absorption of the aqueous phase was measured and shown in figure 47a and the approximate release percentages are shown in figure 47b. The naproxen release percentage was estimated using the absorbance at 330 nm for the aqueous phase versus the standard. Naproxen
was slowly released from the hydrogel of ester 8 in approximately 2-3 days. After 72 h almost all of the naproxen sodium was released from the gel, and the naproxen concentration reached equilibrium in the solution and gel phase. The gel was quite stable even after 18 days, but slowly dissolved as time progressed, after 30 days the gel was almost fully dissolved and turned into a solution.

Figure 46. The gel photos at different time points for compound 8. Final gelator concentration was 1.4 mg/mL. a) 48 h; b) 96 h; c) 248 h; d) 408 h.

Naproxen release was slower for the gel formed by compound 17 in DMSO:H₂O (v/v 1:5) as shown in figure 48. The gel was prepared using 5.0 mg of compound 17 and 0.5 mg of naproxen sodium in 2.0 mL of DMSO:H₂O (v/v 1:5) solution. Afterwards, 2.0 mL of pure water (pH ~7) was placed on top of the gel. The percent release was calculated using the absorbance of the aqueous phase versus the standard at 330 nm. The gel formed by compound 17 facilitated a similar
steady release and it took about four days for half of the naproxen to diffuse from the gel to the aqueous phase.

**Figure 47.** The UV-Vis spectra (a) and release profile (b) of naproxen sodium at different time intervals from the hydrogel of compound 8.
**Figure 48.** The UV-Vis spectra (a) and release profile (b) of naproxen sodium at different time points for the gel formed by compound 17 in DMSO:H₂O (v/v 1:5).
The gel formed by compound 17 remained quite stable throughout the experiment. It is interesting that the gel depicted in figure 49, was very stable and remained intact even up to 28 days in the presence of the added water. This result indicated that the gelators could be useful as soft materials for applications requiring stable gels.

![Figure 49](image1.png)

**Figure 49.** The gel photos at different time points for compound 17. The gelator concentration was 2.5 mg/mL; the initial naproxen concentration was 0.25 mg/mL. a) 9 h; b) 24 h; c) 48 h; d) 200 h.

### 2.2.4 BASE STABILITY STUDIES

These esters are excellent gelators and the resulting gels can be stimuli-responsive if treated with a base or a suitable enzyme to hydrolyze the ester functional group. Stability tests were done under basic conditions for several representative gels. As shown in scheme 3, we treated the gels formed by gelators 8, 16, and 17 in DMSO:H2O (v/v 1:2, 8.0 mg/mL) with basic solutions (pH 12 and pH 13 solutions). Under pH 13 aqueous solutions, the gels turned to liquid within 1 h for compounds 8 and 16, the gel formed by compound 17 turned to liquid after a 4 h treatment of basic solution...
(pH 13). Gelator 17 exhibited increased stability towards base hydrolysis when compared to compounds 8 and 16. The resulting solution was extracted and compound 22 was obtained as the product of the cleavage. This compound was also prepared by a different method and tested for its gelation properties. The diol was soluble in most of the tested solvents, such as ethanol, isopropanol, ethanol and water solutions as well as DMSO and water solutions. However, it showed partial gel formation in water at 20 mg/mL and became soluble upon the addition of water to give a concentration of 10 mg/mL.

![Scheme 3. Cleavage of the esters under basic conditions and the CLogP values of the molecules.](image)

At milder basic conditions, the gels formed by compounds 8 and 16 were stable up to 7 h after exposure to the aqueous solution of the base (pH 12) and started showing decomposition after that. The gel formed by compound 17 however, was more stable; no sign of degradation was observed after 13 days under similar conditions. The base triggered conversion of the lipids to the
corresponding hydroxyl compound 22, indicated that the gels can be chemically converted to solutions. The chemical trigger could also be replaced by an enzymatic trigger using a lipase, and the hydrolysis can be carried out under neutral conditions. This type of controlled release gelators could have significance in materials that require those specific functions.

2.2.5 DYE ABSORPTION STUDIES

The effective gelators 8-21 are simple ester derivatives that were synthesized from glucosamine and they should be biocompatible for certain applications. To test whether they can interact with ionic compounds, toluidine blue dye (TBO) was used as an example and the aromatic ester 18 was selected for the study. Compound 18 formed stable co-gels in the presence of TBO (molar ratio 1:1) at 4.0 mg/mL of compound 18 and 2.4 mg/mL of TBO in DMSO:H₂O (v/v 1:8). This result indicated that the gelator molecules could interact with the dye and form stable gel networks. In order to analyze whether the gel can absorb the dye from aqueous solutions, a gel of compound 18 in DMSO:H₂O (v/v 1:8) was prepared, and an equal volume of toluidine blue solution was added on top of the gel. A few selected photos are shown in figure 50. The 0 h photo shows the gel formed by compound 18 (4.5 mg) in DMSO:H₂O (v/v 1:8, 2.0 mL) at 2.25 mg/mL, then 2.0 mL of a 0.1 mM solution of toluidine blue dye was added on top of the gel. The TBO dye was slowly absorbed by the gel; at 28 h the dye diffused almost to the bottom of the gel, and after 72 h the gel phase showed a homogenous blue color from the dye. The vial was inverted and showed phase separation for the photos at 72 h and 9 days. The gel trapped with TBO dye was very stable and showed very little degradation after 9 days. The sample was left with the aqueous phase on top of the gel and this was still intact after 6 months. This extraordinary stability could be utilized for different applications where gel stability is desirable.
Toluidine blue and other phenothiazines form dimers or higher order aggregations in aqueous solutions and the photophysical behavior of the dyes are important for their applications. The TBO dye exhibited strong dimer absorption at a wavelength of $\lambda_{\text{max}}$ 590 nm and monomer absorption at $\lambda_{\text{max}}$ 626 nm. Both are in the long wavelength regions therefore there is no overlap with the molecular gelators, which allows for a more accurate measurement of the dye concentration. The UV-absorption of toluidine blue into the gel phase was measured at different time intervals, the spectra of the TBO left in the aqueous phase were taken and included in figures 51-55. The standard concentration of the toluidine blue solution was taken using 2 mL of the 0.1 mM solution and this was noted as the maximum absorbance. The dimer was the major form of toluidine blue in solution, before placing the dye solution on top of the gel, only a small amount of the monomer was present. After 2 days, the most dominant peak was the monomer at approximately 626 nm. This indicated that the dimer was absorbed into the 3D network of the gel more preferentially than the monomer and the presence of the gelators caused a reduction in dimerization of the TBO in the aqueous phase. It is possible that the gelator was able to absorb the
dimeric form of TBO due to π-π interactions and hydrophobic forces between the aryl rings of the dye and the molecular gelator. The observation is interesting since it can reduce the dimerization of the dye and confirm that the gel can interact well with cationic compounds or charged ions. The dye absorbing properties can be further studied for the gelators as bio-sorbents and for the removal of dyes from a mixture of solvents.

**Figure 51.** UV-Vis spectra of the toluidine blue solution above the gel of compound 18 at different time intervals. The standard corresponds to the initially added 2.0 mL of a 0.1 mM solution of the toluidine blue dye.
Figure 52. The absorbance profile of toluidine blue by the gel formed by compound 18 at different
time points for the peak at 594 nm in figure 51. The ratios shown were calculated by using 100%-
(the absorbance of the aqueous phase/maximum absorption).

Figure 53. The absorbance profile of toluidine blue that was left in the aqueous solution on top of
the gel formed by compound 18 at different time points for the peak at 594 nm in figure 51. The
ratios were calculated using the absorbance of the aqueous phase/standard absorption.
**Figure 54.** The absorbance profile of toluidine blue by the gel formed by compound 18 at different time points for the peak at 622 nm in figure 51. The ratios shown were calculated using 100% - (the absorbance of aqueous phase/maximum absorption).

**Figure 55.** The absorbance profile of toluidine blue that was left in the aqueous solution on top of the gel formed by compound 18 at different time points for the peak at 622 nm in figure 51. The ratios are calculated using the absorbance of aqueous phase/standard absorption.
All compounds were characterized using $^1$H NMR, $^{13}$C NMR, LC-MS, FT-IR and melting point. The $^1$H, $^{13}$C NMR and FT-IR spectra of a few selected compounds are shown in figures 56-61.

Figure 56. $^1$H and $^{13}$C NMR spectra of compound 9.
Figure 57. $^1$H and $^{13}$C NMR spectra of compound 15.
Figure 58. $^1$H and $^{13}$C NMR spectra of compound 21.
Figure 59. FT-IR spectrum of compound 9.

Figure 60. FT-IR spectra of compound 15.
Figure 61. FT-IR spectra of compound 21.

2.3 CONCLUSIONS
In summary, a series of glucosamine derived esters were prepared, and they were effective LMWGs especially for organic solvents and mixtures of polar organic solvents with water. Both aliphatic and aromatic esters performed very well in organic solvents including toluene and isopropanol, ethylene glycol, and glycerol. Short chain linear aliphatic esters were also effective hydrogelators, while long chain and aromatic esters were not soluble in water. Single ring aromatic esters including furan and substituted benzoic esters were efficient gelators for organic solvents, DMSO/water mixtures, and ethanol/water mixtures. The short chain linear alkyl and cyclohexyl derivatives as well as the aromatic derivatives were more effective than the long chain and t-butyl ester derivatives. Optical microscopy and atomic force microscopy studies showed that the
morphologies of the different gels were mostly fibrous aggregates. The rheological studies for the gelators confirmed their stability and viscoelastic behavior. The steady release of naproxen sodium from the gels of compounds 8 and 17 demonstrated their potential to be used in medical applications as drug delivery systems. Moreover, we showed that these esters can be cleaved under basic conditions and result in a more water-soluble diol, the base triggered reactions could be done via an enzyme and achieve enzymatic cleavage. The stimuli-responsive gelators have the potential to be utilized as controlled delivery carriers for various applications.

2.4 EXPERIMENTAL SECTION

**General method and materials:**

Reagents and solvents were used as they were received from the suppliers. All purifications were carried out using flash column chromatography on 230-400 mesh silica gel with a gradient of solvent systems. NMR analysis was conducted using a 400 MHz Bruker NMR spectrometer. Melting point measurements were carried out using a Fisher-Johns Melting Point apparatus. Rheology measurements were done using a HR-2 Discovery Hybrid Rheometer from TA Instruments and a 25 mm Peltier Plate. UV-Vis experiments were done using a Thermo Scientific Evolution 201 UV-Visible Spectrophotometer.

**Optical microscopy:** A thin smear of the gel was made on a clean glass slide and then observed under an Olympus BX60M optical microscope using an Olympus DP73-1-51 high-performance 17MP digital camera with pixel shifting and Peltier cooling. All the slides were left to air dry for a day or so before taking optical micrographs. The program used to acquire and store the images was CellSens Dimension 1.11.
Atomic force microscopy: The representative gels were prepared approximately 12 h before being placed on the slides. A thin slice of the gel was transferred onto a clean glass slide and then left to air dry for a day or so before being observed under the atomic force microscope (AFM). AFM measurements were carried out using a Veeco Dimension 3100 Atomic Force Microscope. The tips used were Nanosensors silicon AFM probes with a resonant frequency of 340-500 kHz and a force constant of 20-45 Nm$^{-1}$.

Gelation test: Approximately 2 mg of the desired compound was placed in a one-dram vial and 0.1 mL of the gelation solvent or solution was transferred inside the vial to attain a concentration of 20 mg/mL. The vial was heated until the gelator dissolved fully, sometimes the mixture was sonicated to help with dissolving the compound and then left to cool approximately 15 minutes or longer for the gel to form. After this period, if the solution is clear, this is recorded as soluble; if solid reappeared, this is recorded as a precipitate; if the sample formed a gel, then the vial was inverted and if no solvent was flowing this indicated that a stable gel was formed, otherwise it is recorded as an unstable gel. If gelation occurs, another 0.1 mL is added, and the method is repeated until an unstable gel results. The minimum gelation concentration (MGC), the concentration prior to unstable gelation was recorded.

Naproxen trapping and release studies:
Naproxen sodium was dissolved in the desired solvent and this was used to prepare the gel first. For compound 8, naproxen sodium (2.5 mg) was dissolved in 10 mL of H$_2$O and 2 mL of this solution was used to prepare the gel using compound 8 (2.8 mg). The gelator concentration was 1.4 mg/mL and initial naproxen sodium concentration was 0.25 mg/mL. The gel was left at room
temperature for ~12 h, then 2 mL of water (pH ~7) was placed on top of the gel. The UV absorbance of the aqueous phase was taken at different time intervals by transferring the solution to a cuvette and then cautiously returning it to the vial after the measurement. The naproxen final concentration should be 0.125 mg/mL in both aqueous and gel phase if equilibrium has been achieved. A similar protocol was used for other gelators. For compound 17, naproxen sodium (2.5 mg) was dissolved in 10 mL of DMSO:H₂O (v/v 1:5) and 2 mL of this solution was used to make the gel with compound 17 (5.0 mg). The gelator concentration was 2.5 mg/mL, and the initial naproxen concentration was 0.25 mg/mL. The gel was left at room temperature for 12 h, then 2 mL of water (pH ~7) was placed on top of the gel and the absorbance was taken at different time intervals.

**Toluidine blue dye absorption studies:**

A 0.1 mM solution of toluidine blue was prepared by dissolving 6.2 mg of the TBO dye in 200 mL of water. From this solution, 2 mL was placed on top of the gel for the study. The gel was prepared using 4.5 mg of compound 18 in 2.0 mL of DMSO:H₂O (v/v 1:8). The absorbance was taken at different time intervals of the aqueous solution on top of the gel.

**General procedure for the synthesis of esters 7-21**

Compound 6 was synthesized by a previously reported literature procedure.³⁷ In a 50 mL round bottom flask equipped with a drying tube; the headgroup, compound 6 (about 100 mg, 0.24 mmol, 1 equiv.) was dissolved in 4 mL anhydrous acetonitrile. The carboxylic acid (1-1.5 equiv.) was then added to the flask, followed by DIEA (2.0 equiv.). The reaction mixture was stirred for about 6 h at 50 °C. At which time TLC and ¹H NMR spectroscopy were used to monitor the progress of
the reaction. If not complete, the reaction mixture was stirred for longer time. After the starting material was fully converted to the product, the reaction mixture was cooled and concentrated on a rotavap to remove the solvent. The crude product was worked up with DCM and cold 2% NaHCO$_3$ solution then with water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed to obtain the crude product. The crude was then purified by flash column chromatography on silica gel using a gradient of dichloromethane and methanol. The quantities of reagents and characterization data are given below, detailed procedures are not given unless different conditions are used.

**Synthesis of compound 7**

Compound 6 (81.7 mg, 0.20 mmol, 1 equiv.), trimethylacetic acid (26.5 mg, 0.26 mmol, 1.3 equiv.) and DIEA (0.071 mL, 0.40 mmol, 2 equiv.) were added. The reaction mixture was stirred for 6 h at which the $^1$H NMR spectrum showed full conversion. The crude product was purified by column chromatography using hexane/EtOAc from 9:1 to 3:7 to give the desired product as a white solid (75 mg, 87%), $R_f = 0.46$ in 3% MeOH/DCM, mp 176.0-178.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52-7.47 (m, 2H), 7.39-7.33 (m, 3H), 6.44 (d, $J = 8.9$ Hz, 1H), 5.57 (s, 1H), 4.72 (d, $J = 3.9$ Hz, 1H), 4.66 (d, $J = 15.5$ Hz, 1H), 4.59 (d, $J = 15.6$ Hz, 1H), 4.32-4.21 (m, 2H), 3.92 (t, $J = 9.6$ Hz, 1H), 3.86-3.74 (m, 2H), 3.60 (t, $J = 9.1$ Hz, 1H), 3.40 (s, 3H), 1.28 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 176.8, 168.4, 137.0, 128.3, 126.3, 102.0, 98.7, 81.8, 70.5, 68.0, 62.7, 62.4, 55.3, 53.5, 38.8, 27.1. LC-MS m/z calcd. for C$_{21}$H$_{29}$NO$_8$ [M + H]$^+$ 424.2 found 424.2.
Synthesis of compound 8

Compound 6 (103.1 mg, 0.26 mmol, 1 equiv.), valeric acid (0.04 mL, 0.37 mmol, 1.4 equiv.) and DIEA (0.09 mL, 0.52 mmol) were added. The reaction mixture was stirred for 8 h at which the $^1\text{H}$ NMR spectrum showed full conversion. The crude was purified by column chromatography using eluent from pure DCM to 1.5% MeOH/DCM to afford the desired product as a clear solid (97.7 mg, 90%), $R_f = 0.55$ in 3% MeOH/DCM, mp 165.0-167.0 °C. $^1\text{H}$ NMR (400 MHz, CDCl$_3$) $\delta$ 7.52-7.47 (m, 2H), 7.41-7.34 (m, 3H), 6.42 (d, $J = 9.0$ Hz, 1H), 5.57 (s, 1H), 4.73 (d, $J = 3.8$ Hz, 1H), 4.64 (d, $J = 15.5$ Hz, 1H), 4.59 (d, $J = 15.5$ Hz, 1H), 4.32-4.23 (m, 2H), 3.94 (t, $J = 9.6$ Hz, 1H), 3.86-3.74 (m, 2H), 3.60 (t, $J = 9.1$ Hz, 1H), 3.41 (s, 3H), 2.44 (t, $J = 7.4$ Hz, 2H), 1.71-1.62 (m, 2H), 1.45-1.34 (m, 2H), 0.95 (t, $J = 7.3$ Hz, 3H); $^{13}\text{C}$ NMR (100 MHz, CDCl$_3$) $\delta$ 172.2, 168.2, 137.0, 128.3, 126.3, 102.0, 98.7, 81.9, 70.4, 68.2, 62.8, 62.4, 55.4, 53.5, 33.7, 26.9, 22.2, 13.6. LC-MS m/z calcd. for C$_{21}$H$_{29}$NO$_8$ [M + H]$^+$ 424.2 found 424.2.

Synthesis of compound 9

(Compounds 9, 12, 14, 19 were made by Paige Kozlowski who collaborated on my project)

Compound 6 (77.5 mg, 0.19 mmol, 1 equiv.), 6-heptynoic acid (27.2 mg, 0.22 mmol, 1 equiv.) and DIEA (68 µL, 0.39 mmol, 2 equiv.) were added. The reaction mixture was stirred at 60 °C for 6 h at which the $^1\text{H}$ NMR and TLC showed full conversion. The crude product was purified by column chromatography using eluent from pure DCM to 3% MeOH/DCM to afford the desired product as a white solid (79.9 mg, 93%), $R_f = 0.4$ in 3% MeOH/DCM, mp 167.0-169.0 °C. $^1\text{H}$ NMR (400 MHz, CDCl$_3$) $\delta$ 7.51-7.46 (m, 2H), 7.39-7.34 (m, 3H), 6.39 (d, $J = 8.9$ Hz, 1H), 5.56 (s, 1H), 4.75 (d, $J = 3.8$ Hz, 1H), 4.67-4.58 (m, 2H), 4.32-4.23 (m, 2H), 3.98-3.91 (m, 1H), 3.85-3.74 (m, 2H), 3.62-3.56 (m, 1H), 3.42 (s, 3H), 2.47 (t, $J = 7.4$ Hz, 2H), 2.24 (dt, $J = 7.0$, 2.6 Hz,
Synthesis of compound 10

Compound 6 (94.4 mg, 0.23 mmol, 1 equiv.), cyclohexane carboxylic acid (39.3 mg, 0.31 mmol, 1.3 equiv.) and DIEA (0.08 mL, 0.46 mmol, 2 equiv.) were added. The reaction mixture was stirred for 7 h at which the $^1$H NMR spectrum and TLC showed full conversion. The crude was purified via column chromatography using hexane/EtOAc from 8.5:1 to 2:8 to produce the desired product as a white solid (91.4 mg, 87%), $R_f$ = 0.40 in 3% MeOH/DCM, mp 174.0-176.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52-7.46 (m, 2H), 7.40-7.33 (m, 3H), 6.42 (d, $J = 9.0$ Hz, 1H), 5.57 (s, 1H), 4.73 (d, $J = 3.8$ Hz, 1H), 4.66 (d, $J = 15.7$ Hz, 1H), 4.58 (d, $J = 15.7$ Hz, 1H), 4.32-4.21 (m, 2H), 3.94 (t, $J = 9.4$ Hz, 1H), 3.86-3.73 (m, 2H), 3.60 (t, $J = 9.1$ Hz, 1H), 3.41 (s, 3H), 2.48-2.38 (m, 1H), 2.02-1.91 (m, 2H), 1.84-1.74 (m, 2H), 1.73-1.63 (m, 1H), 1.57-1.44 (m, 2H), 1.41-1.19 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.3, 168.4, 137.0, 128.3, 126.3, 102.0, 98.7, 81.9,70.6, 68.8, 62.6, 62.4, 55.3, 53.6, 42.9, 29.0, 28.9, 25.6, 25.3, 25.3. LC-MS m/z calcd. for C$_{23}$H$_{30}$NO$_8$ [M + H]$^+\ 448.2$ found 448.2.

Synthesis of compound 11

Compound 6 (100.7 mg, 0.25 mmol, 1 equiv.), palmitic acid (68.7 mg, 0.27 mmol, 1 equiv.) followed by DIEA (0.09 mL, 0.52 mmol, 2 equiv.) were added. The reaction mixture was left to stir for 7 h at which the TLC and $^1$H NMR demonstrated full conversion. The crude was purified via column chromatography using hexane/acetone to produce the desired product as a white solid
(88.3 mg, 61%) as the desired product. Rf = 0.63 in 3% MeOH/DCM, mp 138.0-140.0 °C. 1H NMR (400 MHz, CDCl3) δ 7.52-7.47 (m, 2H), 7.40-7.34 (m, 3H), 6.42 (d, J = 9.0 Hz, 1H), 5.57 (s, 1H), 4.74 (d, J = 3.8 Hz, 1H), 4.64 (d, J = 15.2 Hz, 1H), 4.59 (d, J = 15.2 Hz, 1H), 4.32-4.23 (m, 2H), 3.94 (t, J = 9.3 Hz, 1H), 3.86-3.73 (m, 2H), 3.60 (t, J = 9.1 Hz, 1H), 3.42 (s, 3H), 2.43 (t, J = 7.5 Hz, 2H), 1.73-1.62 (m, 2H), 1.41-1.14 (m, 24 H), 0.88 (t, J = 7.1 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 172.2, 168.2, 137.0, 128.3, 126.3, 102.0, 98.7, 81.9, 70.3, 68.8, 62.8, 62.4, 55.4, 53.5, 34.0, 31.90, 29.7, 29.6, 29.6, 29.3, 29.11, 24.8, 22.7, 14.1. LC-MS m/z calcd. for C32H51NO8 [M + H]+ 578.4, found 578.3.

**Synthesis of compound 12**

Compound 6 (101 mg, 0.25 mmol, 1 equiv.), heptadecanoic acid (68 mg, 0.25 mmol, 1 equiv.) and DIEA (80 µL, 0.47 mmol, 2 equiv.) were added. The reaction mixture was stirred for 24 h at which the 1H NMR spectrum and TLC confirmed full conversion. The crude was purified by column chromatography using eluent from pure DCM to 2% MeOH/DCM to yield the desired product as a white solid (101 mg, 69%), Rf = 0.5 in 3% MeOH/DCM, mp 142.0-144.0 °C. 1H NMR (400 MHz, CDCl3) δ 7.52-7.46 (m, 2H), 7.39-7.34 (m, 3H), 6.41 (d, J = 8.9 Hz, 1H), 5.57 (s, 1H), 4.74 (d, J = 3.8 Hz, 1H), 4.67-4.57 (m, 2H), 4.31-4.24 (m, 2H), 3.94 (t, J = 9.6 Hz, 1H), 3.85-3.75 (m, 2H), 3.64-3.57 (m, 1H), 3.41 (s, 3H), 2.43 (t, J = 7.6 Hz, 2H), 1.72-1.62 (m, 2H), 1.39-1.21 (m, 26H), 0.88 (t, J = 6.8 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 172.2, 168.2, 137.0, 129.3, 128.3, 126.3, 102.0, 98.7, 81.9, 70.4, 68.8, 62.8, 62.4, 55.4, 53.5, 34.0, 31.9, 29.7, 29.6, 29.4, 29.34, 29.25, 29.1, 24.8, 22.7, 14.1. LC-MS m/z calcd. for C33H53NO8Na [M + Na]+ 614.4, found 614.4.
Synthesis of compound 13

Compound 6 (100.1 mg, 0.25 mmol, 1 equiv.), eicosanoic acid (80.3 mg, 0.26 mmol, 1 equiv.) and DIEA (0.09 mL, 0.52 mmol, 2 equiv.) were added. The reaction mixture was stirred for 7 h at which the $^1$H NMR spectrum and TLC confirmed full conversion. The crude was purified by column chromatography using eluent from 100% DCM to 1.5% MeOH/DCM to give the desired product as a white solid (122 mg, 78%), $R_f$ =0.50 in 3% MeOH/DCM, mp 145.0-147.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52-7.46 (m, 2H), 7.40-7.33 (m, 3H), 6.40 (d, $J = 9.0$ Hz, 1H), 5.57 (s, 1H), 4.73 (d, $J = 3.8$ Hz, 1H), 4.64 (d, $J = 15.5$ Hz, 1H), 4.59 (d, $J = 15.5$ Hz, 1H), 4.33-4.22 (m, 2H), 3.93 (t, $J = 9.4$ Hz, 1H), 3.85-3.73 (m, 2H), 3.59 (t, $J = 9.1$ Hz, 1H), 3.41 (s, 3H), 2.42 (t, $J = 7.6$ Hz, 2H), 1.73-1.61 (m, 2H), 1.40-1.15 (m, 32H), 0.88 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.2, 168.2, 137.0, 129.3, 128.3, 126.3, 102.0, 98.7, 81.9, 70.4, 68.8, 62.8, 62.4, 55.4, 53.5, 34.0, 31.9, 29.7, 29.6, 29.4, 29.3, 29.2, 29.1, 24.8, 22.7, 14.1.

Synthesis compound 14

Compound 6 (97 mg, 0.24 mmol, 1 equiv.), 2-furoic acid (27 mg, 0.240 mmol, 1 equiv.) and DIEA (78 µL, 0.45 mmol, 2 equiv.) were added. The reaction mixture was stirred for 24 h at which the $^1$H NMR spectrum and TLC confirmed full conversion. The crude was purified by column chromatography using eluent from pure DCM to 3% MeOH/DCM to afford the desired product as a white solid (87 mg, 84%), $R_f$ =0.35 in 5% MeOH/DCM, mp 229.0-231.0 °C. $^1$H NMR (400 MHz, CDCl$_3$ + d$_4$-MeOH) $\delta$ 7.61 (d, $J = 1.5$ Hz, 1H), 7.50-7.41 (m, 2H), 7.36-7.29 (m, 3H), 7.28 (d, $J = 3.6$ Hz, 1H), 6.74 (d, $J = 9.0$ Hz, 1H), 6.56-6.53 (m, 1H), 5.53 (s, 1H), 4.83-4.72 (m, 2H), 4.70 (d, $J = 3.8$ Hz, 1H), 4.28-4.14 (m, 2H), 3.86 (t, $J = 9.7$ Hz, 1H), 3.81-3.70 (m, 2H), 3.56 (t, $J = 9.0$ Hz, 1H), 3.34 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$ + d$_4$-MeOH) $\delta$ 167.7,
Synthesis of compound 15

Compound 6 (102.7 mg, 0.26 mmol, 1 equiv.), benzoic acid (48.8 mg, 0.40 mmol, 1.5 equiv.) and DIEA (0.09 mL, 0.52 mmol, 2 equiv.) were added. The reaction mixture was stirred for 7 h at which the $^1$H NMR spectrum and TLC confirmed full conversion. The crude was purified by column chromatography using eluent from pure DCM to 1.5% MeOH/DCM to give the desired product as a white solid (95.5 mg, 83%), Rf = 0.38 in 3% MeOH/DCM. mp 223.0-225.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.07 (d, $J$ = 8.0, 2H), 7.67-7.58 (m, 1H), 7.54-7.43 (m, 4H), 7.40-7.32 (m, 3H), 6.56 (d, $J$ = 9.0 Hz, 1H), 5.56 (s, 1H), 4.90 (d, $J$ = 15.6 Hz, 1H), 4.83 (d, $J$ = 15.6 Hz, 1H), 4.74 (d, $J$ = 3.2 Hz, 1H), 4.36-4.23 (m, 2H), 3.95 (t, $J$ = 9.5 Hz, 1H), 3.86-3.72 (m, 2H), 3.61 (t, $J$ = 8.5 Hz, 1H), 3.35 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 168.1, 165.2, 137.1, 133.8, 129.7, 129.2, 128.7, 128.3, 126.3, 102.0, 98.8, 81.8, 70.4, 68.8, 63.4, 62.5, 55.4, 53.7. LC-MS m/z calcd. for C$_{23}$H$_{26}$NO$_8$ [M + H]$^+$ 444.2, found 444.2.

Synthesis of compound 16

Compound 6 (80.4 mg, 0.20 mmol, 1 equiv.), 3-chlorobenzoic acid (39.3 mg, 0.22 mmol, 1 equiv.) and DIEA (0.07 mL, 0.40 mmol, 2 equiv.) were added. The reaction mixture was stirred for 7 h at which the $^1$H NMR spectrum and TLC confirmed full conversion. The crude was purified by column chromatography using eluent from pure DCM to 1% MeOH/DCM to afford the desired product as a white solid (82.3 g, 86%), Rf = 0.43 in 3% MeOH/DCM. mp 233.0-235.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.04 (t, $J$ = 1.8 Hz, 1H), 8.00-7.94 (m, 1H), 7.64-7.59 (m, 1H), 7.52-
7.42 (m, 3H), 7.40-7.34 (m, 3H), 6.50 (d, \( J = 9.1 \) Hz, 1H), 5.57 (s, 1H), 4.86 (s, 2H), 4.76 (d, \( J = 3.8 \) Hz, 1H), 4.34-4.24 (m, 2H), 3.96 (t, \( J = 9.6 \) Hz, 1H), 3.86-3.73 (m, 2H), 3.61 (t, \( J = 9.1 \) Hz, 1H), 3.40 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 167.7, 137.0, 134.9, 133.8, 130.7, 130.1, 129.7, 129.3, 128.3, 127.9, 126.3, 102.0, 98.7, 81.8, 70.6, 68.8, 63.7, 62.5, 55.4, 53.6. LC-MS m/z calcd. for C\(_{23}\)H\(_{24}\)ClNO\(_8\) [M + H\(^+\)] 479.1, found 479.1.

**Synthesis of compound 17**

Compound 6 (80.3 mg, 0.20 mmol, 1 equiv.), 4-methoxybenzoic acid (31.4 mg, 0.21 mmol, 1 equiv.) and DIEA (0.071 mL, 0.41 mmol, 2 equiv.) were added. The reaction mixture was stirred for 6 h at which the \(^1\)H NMR spectrum and TLC confirmed full conversion. The crude was purified by column chromatography using eluent from pure DCM to 1% MeOH/DCM to give the desired product as a white solid (81 mg, 86%), \( R_f = 0.5 \) in 5% MeOH/DCM. mp 236.0-238.0 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.03 (d, \( J = 8.8 \) Hz, 2H), 7.52-7.46 (m, 2H), 7.40-7.33 (m, 3H), 6.97 (d, \( J = 8.9 \) Hz, 2H), 6.54 (d, \( J = 9.0 \) Hz, 1H), 5.57 (s, 1H), 4.87 (d, \( J = 15.2 \) Hz, 1H), 4.79 (d, \( J = 15.2 \) Hz, 1H), 4.74 (d, \( J = 3.9 \) Hz, 1H), 4.33-4.23 (m, 2H), 3.94 (t, \( J = 9.6 \) Hz, 1H), 3.89 (s, 3H), 3.85-3.73 (m, 2H), 3.61 (t, \( J = 9.0 \) Hz, 1H), 3.35 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 168.4, 164.9, 164.1, 137.1, 131.9, 129.3, 128.3, 126.3, 114.0, 102.0, 98.8, 81.8, 70.6, 68.8, 63.2, 62.4, 55.5, 55.4, 53.6. LC-MS m/z calcd. for C\(_{24}\)H\(_{27}\)NO\(_9\) [M + H\(^+\)] 474.2, found 474.2.

**Synthesis of compound 18**

Compound 6 (100.2 mg, 0.26 mmol, 1 equiv.), 4-nitrobenzoic acid (42.7 mg, 0.26 mmol, 1 equiv.) and DIEA (0.09 mL, 0.52 mmol, 2 equiv.) were added. The reaction mixture was stirred for 23.5 h at which the \(^1\)H NMR spectrum and TLC confirmed full conversion. The crude was purified by
column chromatography using eluent from pure DCM to 1% MeOH/DCM to yield the desired product as a white solid (108.6 g, 89%), R<sub>f</sub> = 0.38 in 5% MeOH/DCM. mp 241.0-243.0 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.34 (d, J = 8.8 Hz, 2H), 8.25 (d, J = 8.8 Hz, 2H), 7.52-7.45 (m, 2H), 7.40-7.32 (m, 3H), 6.35 (d, J = 8.8 Hz, 1H), 5.57 (s, 1H), 4.90 (s, 2H), 4.77 (d, J = 3.8 Hz, 1H), 4.36-4.24 (m, 2H), 3.95 (t, J = 9.6 Hz, 1H), 3.84-3.74 (m, 2H), 3.65-3.55 (m, 1H), 3.39 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 167.2, 163.6, 151.0, 137.0, 134.3, 130.9, 129.3, 128.3, 126.3, 123.8, 102.0, 98.7, 81.8, 70.4, 68.8, 63.9, 62.5, 55.4, 53.6. LC-MS m/z calcd. for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O<sub>10</sub> [M + H]<sup>+</sup> 489.2, found 489.2.

**Synthesis of compound 19**

Compound 6 (103 mg, 0.26 mmol, 1 equiv.), 4-bromobenzoic acid (51 mg, 0.25 mmol, 1 equiv.) and DIEA (81 µL, 0.47 mmol, 2 equiv.) were added. The reaction mixture was stirred for 8 h at which the <sup>1</sup>H NMR spectrum and TLC confirmed full conversion. The crude was purified by column chromatography using eluent from pure DCM to 2% MeOH/DCM to yield the desired product as a white solid (98 mg, 74%), R<sub>f</sub> = 0.3 in 3% MeOH/DCM. mp 221.0-223.0 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.95-7.91 (m, 2H), 7.66-7.61 (m, 2H), 7.51-7.45 (m, 2H), 7.40-7.33 (m, 3H), 6.47 (d, J = 8.9 Hz, 1H), 5.56 (s, 1H), 4.90-4.79 (m, 2H), 4.74 (d, J = 3.8 Hz, 1H), 4.31-4.24 (m, 2H), 3.94 (t, J = 9.6 Hz, 1H), 3.83-3.73 (m, 2H), 3.64-3.55 (m, 1H), 3.36 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 167.8, 164.6, 137.0, 132.1, 131.2, 129.3, 129.1, 128.3, 127.8, 126.3, 102.0, 98.7, 81.8, 70.3, 68.8, 63.5, 62.5, 55.4, 53.7. LC-MS m/z calcd. for C<sub>23</sub>H<sub>25</sub>N08Br [M + H]<sup>+</sup> 522.1, found 522.1.
Synthesis of compound 20

Compound 6 (75.0 mg, 0.19 mmol, 1 equiv.) was dissolved in N, N-dimethylformamide (3 mL), 1-naphthylacetic acid (56.7 mg, 0.30 mmol, 1.6 equiv.) and potassium carbonate (53.7 mg, 0.39 mmol, 2 equiv.) were added. The reaction mixture was stirred for 12 h at rt after which the $^1$H NMR spectrum and TLC confirmed full conversion. The crude was purified by column chromatography using eluent from pure DCM to 3% MeOH/DCM to afford the desired 1-naphthylacetate product as a white solid (78.8 mg, 83%), $R_f = 0.50$ in 3% MeOH/DCM. mp 183.0-185.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.03 (d, $J = 8.4$ Hz, 1H), 7.91 (d, $J = 7.5$ Hz, 1H), 7.88 - 82 (m, 1H), 7.64-7.44 (m, 6H), 7.44-7.35 (m, 3H), 5.84 (d, $J = 9.2$ Hz, 1H), 5.53 (s, 1H), 4.70-4.50 (m, 3H), 4.28-4.21 (m, 1H), 4.20 (d, $J = 3.0$ Hz, 2H), 4.11-4.03 (m, 1H), 3.77-3.62 (m, 2H), 3.51-3.42 (m, 1H), 3.41-3.33 (m, 1H), 3.22 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.7, 167.5, 137.1, 134.0, 131.9, 129.7, 129.3, 129.0, 128.5, 128.3, 128.2, 126.8, 126.3, 126.3, 126.2, 125.6, 123.5, 101.9, 98.5, 81.7, 69.7, 68.8, 63.1, 62.3, 55.2, 53.1, 39.1. LC-MS m/z calcd. for C$_{28}$H$_{29}$NO$_8$ [M + H]$^+$ 508.2, found 508.2.

Synthesis of compound 21

Compound 6 (131.3 mg, 0.33 mmol, 1 equiv.) was dissolved in N, N-dimethylformamide (3 mL), 2-naphthylacetic acid (94.5 mg, 0.51 mmol, 1.5 equiv.) and DIEA (0.11 mL, 0.63 mmol, 2 equiv.) were added. The reaction mixture was stirred for 24 h at rt after which the $^1$H NMR spectrum and TLC confirmed full conversion. The crude was purified by column chromatography using eluent from pure DCM to 2% MeOH/DCM to achieve the desired 2-naphthylacetate product as a white solid (129.5 mg, 78%), $R_f = 0.4$ in 3% MeOH/DCM. mp 154.0-156.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.89-7.75 (m, 4H), 7.57-7.33 (m, 8H), 6.00 (d, $J = 8.9$ Hz, 1H), 5.51 (s, 1H), 4.63 (d, $J$
= 5.2 Hz, 2H), 4.58 (d, $J = 3.8$ Hz, 1H), 4.23 (dd, $J = 10.2$, 4.7 Hz, 1H), 4.14-4.06 (m, 1H), 3.91 (s, 2H), 3.71 (t, $J = 10.2$ Hz, 1H), 3.64-3.55 (m, 1H), 3.49-3.40 (m, 2H), 3.16 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.7, 167.6, 137.2, 133.5, 132.6, 130.7, 129.3, 128.7, 128.3, 128.1, 127.7, 127.6, 127.0, 126.6, 126.3, 101.9, 98.5, 81.7, 69.6, 68.8, 63.0, 62.3, 55.1, 53.3, 41.5. LC-MS m/z calcd. for C$_{28}$H$_{29}$NO$_8$ [M + H]$^+$ 508.2, found 508.2.
CHAPTER 3

THE SYNTHESIS AND SELF-ASSEMBLING PROPERTIES OF GLYCOLIPIDS CONTAINING ESTER, ETHER AND AMINE FUNCTIONAL GROUPS

PREFACE
This chapter is adapted from the following manuscript:


3.1 INTRODUCTION

Low molecular weight gelators (LMWGs) are a multifaceted group of compounds that have many applications in today’s world. These compounds are organic molecules that have a mass of less than 2000-3000 Da and are further classified as low molecular-weight hydrogelators (LMWHs) or low molecular weight organogelators or (LMOGs). The gels are typically composed of a majority of liquid with just a small amount of the gelators, which form 3-D networks that immobilize the solvents. Among the different classes of LMWGs, carbohydrates have been used widely as structure templates to design and synthesize effective LMWGs. Sugar-based compounds can be altered at various positions with a wide selection of functional groups to investigate their impact on the gelation process and obtain advanced functional materials. Sugar-based gelators hold great promise in many areas to help alleviate or solve problems as they are biodegradable and biocompatible. They are made from natural resources that can build intricate networks via gelation and produce smart materials. Another fascinating aspect of these supramolecular carbohydrate-based gelators is that they can help to influence biological processes...
such as cell signaling, inflammation and immune response as well as interactions with proteins and other biological fluids.\textsuperscript{71,221,222}

Enzymes are proteins that catalyze chemical and biochemical reactions and are known for their high specificity and efficiency.\textsuperscript{159} They have been employed by industries to carry out biotransformations, but pose a few challenges in the field; they cannot be recycled properly and have low stability. However, researchers have proven that immobilized enzymes can perform better because they are more stable, perform with a higher efficiency and can be recycled after the catalytic process.\textsuperscript{159,223} This allows for lower production costs and continuous flow methods within an industrial setting.\textsuperscript{223} Entrapment is one of the most common methods for immobilization because it allows for the enzyme to be free within the gel matrix without occupancy of its active site.\textsuperscript{159,160}Whilst research on materials used to immobilized enzymes are still ongoing, many studies in the literature focus on beads made from polymers or silica matrices.\textsuperscript{159,224,225} Low molecular weight gelators are an untapped resource for enzyme immobilization and should not be overlooked. Previously, we have reported that the glucose derivative 1 in figure 62 was an effective gelator.\textsuperscript{226} We have found that various alkyl and aryl amide derivatives 2 were versatile LMWGs. Compound 2a contains a tertiary amino functional group and formed a hydrogel at 0.4 wt %.\textsuperscript{227}
While studying sugar derivatives as molecular gelators and their applications as biomaterials, we became interested in finding out the effect of charged functional groups towards molecular assemblies. Cationic gelators have gained attention and have demonstrated potential use for dye removal, drug delivery and enzyme immobilization. Initial reports of organic salts were made by the Dastidar Research group in the early 2000’s. They were examining the X-ray crystal structure of several new organic salts but stumbled on a gel during the recrystallization process for the imidazolium hydrogen cyclobutane-1,1-dicarboxylate salt in nitrobenzene. This initial breakthrough paved the way for widespread research on gelators from organic salts. Since then, salt-based gelators have gained increased attention in the field of materials science for many applications. They have been utilized as gelators for ionic liquids, conductivity, host-guest interactions, dye absorption, oil spill clean-up and biomedical applications. Herein, we designed and synthesized sugar derivatives containing amino, ether and ester functional groups and studied their gelation properties as well as applications for drug delivery and enzyme immobilization. The design of the molecules features a longer alkyl chain from the gelators in chapter 2, to increase the hydrophobicity from the headgroup to the acyl group and other polar
substituents. We believe this will probe the influence of increasing the hydrophobic functions in the acyl chain. Introduction of the ether functional group could possibly allow for the gelators to be chemically inert for enzyme immobilization and dye absorption. One specific amine derivative was utilized to develop a series of ammonium salts and then studied for their gelation properties.

3.2 RESULTS AND DISCUSSION

The monosaccharide head group 7 in scheme 4 was employed to create a series of long chain esters and ethers as shown in schemes 5 and 6. They were synthesized by reacting the head group with different carboxylic acids and alcohols in the presence of potassium carbonate or DIEA (N, N, -Diisopropylethylamine) at 70 °C. The reactions gave moderate to high yields and most of the compounds formed gels in several of the tested solvents. A series of amines shown in scheme 7 were also synthesized from head group 7 utilizing both aliphatic and aromatic amines. The reactions also gave moderate to good yields.

Scheme 4. Synthesis of the carbohydrate building block.
Scheme 5. Synthesis of the carbohydrate esters.

3.2.1 GELATION PROPERTIES OF THE SYSTEMS

The ester and ether derivatives were the best performing gelators as shown in tables 4 and 5. The esters readily formed gels in ethylene glycol, water and aqueous solutions of water with DMSO and ethanol. The most effective gelator overall and in the ester series, was the hydrogel formed by compound 10 at 1.2 mg/mL. On the other hand, the ethers were efficient gelators for ethylene glycol, glycerol and aqueous solutions of water with DMSO and ethanol. A few gels also formed in polar solvents like isopropanol and ethanol as well as non-polar solvents like toluene. The best performing ether was compound 15 which formed a translucent gel in DMSO:H₂O (v/v 1:2) at a concentration of 1.43 mg/mL.

Scheme 7. Synthesis of the carbohydrate-based amines.
Table 4. Gelation test results of the esters.

<table>
<thead>
<tr>
<th>Cpd. #</th>
<th>Tol</th>
<th>i-PrOH</th>
<th>EtOH</th>
<th>EG</th>
<th>Glycerol</th>
<th>EtOH: H₂O (1:2)</th>
<th>EtOH: H₂O (1:1)</th>
<th>DMSO: H₂O (1:2)</th>
<th>DMSO: H₂O (1:1)</th>
<th>H₂O</th>
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<td>S</td>
<td>S</td>
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<td>S</td>
<td>G6.7</td>
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<td>P</td>
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<td>G4.0</td>
<td>G5.0</td>
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<td>G6.7</td>
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</tr>
<tr>
<td>13</td>
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<td>P</td>
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<td>P</td>
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<tr>
<td>14</td>
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<td>PG</td>
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<td>G5.0</td>
<td>G6.7</td>
<td>PG</td>
<td>G2.2</td>
<td>G3.3</td>
<td>PG</td>
</tr>
</tbody>
</table>

All compounds were tested starting from 20 mg/mL. G, stable gel at room temperature, the numbers are MGC (MGCs) in mg/mL; P, precipitation; S, soluble; I, insoluble; PG, partial gel; T, translucent; C, clear; O, opaque. Hex-hexane, Tol-toluene, EG-ethylene glycol, TEG-triethylene glycol. All compounds were insoluble in hexane but soluble in TEG, compound 10 formed a precipitate in hexane.
Table 5. Gelation tests results of the ethers

<table>
<thead>
<tr>
<th>Cpd. #</th>
<th>Tol</th>
<th>i-PrOH</th>
<th>EtOH</th>
<th>EG</th>
<th>Glycero1</th>
<th>EtOH: H2O (1:2)</th>
<th>EtOH: H2O (1:1)</th>
<th>DMSO: H2O (1:2)</th>
<th>DMSO: H2O (1:1)</th>
<th>H2O</th>
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<tbody>
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<td>G20.0&lt;sub&gt;T&lt;/sub&gt;</td>
<td>G10.0&lt;sub&gt;O&lt;/sub&gt;</td>
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<td>G2.9&lt;sub&gt;O&lt;/sub&gt;</td>
<td>G1.7&lt;sub&gt;O&lt;/sub&gt;</td>
<td>PG</td>
<td>G3.3&lt;sub&gt;O&lt;/sub&gt;</td>
<td>G1.4&lt;sub&gt;O&lt;/sub&gt;</td>
<td>G4.0&lt;sub&gt;O&lt;/sub&gt;</td>
<td>PG</td>
</tr>
<tr>
<td>16</td>
<td>PG</td>
<td>PG</td>
<td>P</td>
<td>G4.0&lt;sub&gt;T&lt;/sub&gt;</td>
<td>G2.5&lt;sub&gt;T&lt;/sub&gt;</td>
<td>I</td>
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<td>I</td>
</tr>
<tr>
<td>17</td>
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<td>PG</td>
<td>G20.0&lt;sub&gt;T&lt;/sub&gt;</td>
<td>G4.0&lt;sub&gt;T&lt;/sub&gt;</td>
<td>G5.0&lt;sub&gt;T&lt;/sub&gt;</td>
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<td>I</td>
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<td>G2.2&lt;sub&gt;O&lt;/sub&gt;</td>
<td>P</td>
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</tbody>
</table>

All compounds were soluble in triethylene glycol and insoluble in hexane.

The syntheses of various amine derivatives are shown in schemes 7. After purification, the gelation properties of the compounds were tested, and the results are summarized in table 6. The aliphatic amines were mostly soluble, but the aryl amines formed gels in several of the tested solvents. The aniline derivative 21 was the most versatile gelator forming gels in six of the tested solvents, with the lowest minimum gelation concentration (MGC). Most interestingly, the hydrogel formed by the propionic ester 10 at 0.12 wt %, also formed a co-gel with the pyridinium salt 23 (1:1 mole ratio of the two compounds) in water at a MGC of 0.022 mol/L. Figure 63 shows a few representative gel photos and the morphologies are depicted in figure 64. The optical microscope images taken under brightfield for both compounds 14 and 18 showed intertwined fibers that made up the bulk of the gel. Compound 18 had longer continuous fibers while compound 14 had shorter fibers in the network.
Table 6. Gelation test results of the amines.

<table>
<thead>
<tr>
<th>Cpd. #</th>
<th>Tol</th>
<th>i-PrOH</th>
<th>EtOH</th>
<th>E</th>
<th>Glycerol</th>
<th>EtOH: H₂O (1:2)</th>
<th>EtOH: H₂O (1:1)</th>
<th>DMSO: H₂O (1:2)</th>
<th>DMSO: H₂O (1:1)</th>
<th>H₂O</th>
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<tr>
<td>19</td>
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<td>S</td>
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<td>P</td>
<td>S</td>
<td>S</td>
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<td>S</td>
<td>S</td>
<td>S</td>
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</tr>
<tr>
<td>21</td>
<td>PG</td>
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<td>S</td>
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<td>G4.0₀</td>
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<td>G2.9₀</td>
<td>G5.0₁</td>
<td>G20.0₀</td>
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<tr>
<td>22</td>
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<td>G20.0₀</td>
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<tr>
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<td>G40.0₀</td>
<td>S</td>
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<td>S</td>
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</tbody>
</table>

All compounds were insoluble in hexane and soluble in TEG.

Figure 63. Gel photos: a) Opaque gel of compound 12 in DMSO:H₂O (v/v 1:2) at 1.70 mg/mL; b) Opaque gel of compound 16 in DMSO:H₂O (v/v 1:2) at 2.00 mg/mL.
Figure 64. Optical micrographs of a few representative gels under brightfield. a) Optical micrograph of compound 14 in DMSO:H₂O (1:2) with a concentration of 2.0 mg/mL, Scale bar (10µm); b) & c) Optical micrograph of compound 18 in DMSO:H₂O (1:1) at a concentration of 2.0 mg/mL, Scale bar (20 & 10µm) respectively. d) Optical micrograph of compound 10 in H₂O at a concentration of 1.2 mg/mL, Scale bar (10µm).

3.2.2 DRUG RELEASE STUDIES

Compound 10 formed a hydrogel and so it was tested for its potential to be utilized in drug delivery and hydroxychloroquine was utilized as the model drug. In the experiment, 20 mg of compound 10 was used to make a hydrogel in 2 mL of a hydroxychloroquine solution (0.025 mg of
hydroxychloroquine in 2.0 mL of water). The gel was allowed to sit for 50 minutes then 2.0 mL of phosphate buffered saline (pH 7-7.4) was placed on top of the gel; it was placed in an incubator at 37 °C and the absorbance of the aqueous layer was recorded overtime. The hydroxychloroquine release percentage was estimated using the absorbance at 343 nm for the aqueous phase versus the standard. The UV-Vis spectra shown in figure 65, indicated the slow release of hydroxychloroquine overtime into the aqueous phase on top of the gel. From the spectra, it is clear that the drug was released slowly from the gel and after approximately 119 h, the hydroxychloroquine concentration reached equilibrium in the gel and the solution phase. This demonstrated that the hydrogel facilitated a slow and sustained release of the drug overtime, showing it has the potential to be utilized as a drug delivery vehicle. The gel photographs shown in figure 65 also indicated that the gel remained stable throughout the process. This is essential for the sustained release because if the gel is not stable for a long period of time, then decomposition will interfere with the slow and steady release of the drug.
Figure 65. The UV-Vis spectra (a) and release profile (b) of hydroxychloroquine at different time points from the hydrogel of compound 10 with gel photos.
3.2.3 LIPASE AND BASE DEGRADATION STUDIES

The lipase triggered studies were done with lipase type II crude from porcine pancreas. In short, the gels were made with 4 mg of compounds 10, 11 and 12 in 0.5 mL of DMSO:H₂O, v/v 1:5 was added to make the gel (two gels were made), the gels were then transferred to a scintillation vial which was heated in an oil bath at 120-140 °C. In the case of compound 10, 0.5 mL of water was used to make the gel. After 24 h, 0.5 mL of lipase solution was added to one of the vials and phosphate buffer (pH 7.29) to the other to represent the control. The gels were placed in an incubator and allowed to stir at 37 °C and 95 rpm. They were observed every hour to record any decomposition that might occur. After the gels are broken down, the resulting compound was then extracted with 2 mL of DCM and a proton NMR spectrum was taken. The lipase amount was calculated individually based on the molar equivalent necessary for the reaction. Interestingly, even though the gel volume was reduced in the vials, the hydrolyzed compound depicted in scheme 8 was not seen on the proton NMR spectra. Compound 11 was extracted after approximately 8.5 days and compounds 12 and 10 after nearly 18.5 days. These results may be due to the molecules not being able to fit into the binding site of the lipase enzyme for it to act on the esters.

On the other hand, the compounds were responsive to basic conditions, the gels were made similarly as in the lipase studies but were utilized 2 h after they were made. 0.5 mL of pH 12 and 13 solutions were added to the vials at room temperature and the gels were observed every hour to record any decomposition that occurred. After the gels were broken down the resulting compound was extracted with 2 mL of DCM and a proton NMR spectrum was taken. For compound 10, the gels were broken down in pH 12 after 4 days and 26 h and in pH 13 after approximately 24 h. Unfortunately, even though the gels were reduced the NMR spectra did not really show the
presence of the hydrolyzed compound. After approximately 18 days, the vials with gels from compounds 12 and 11 were placed in a shaker incubator for 4 h and 7 minutes at 50 °C and 95 rpm but the results were the same. This shows that the longer chain esters are more stable under basic conditions and in the presence of lipase when compare to their short chain counterparts that were reported in chapter 2.

**Scheme 8.** Cleavage of the long chain esters in the presence of lipase.

### 3.2.4 ENZYME IMMobilIZATION STUDIES

In order to investigate if the gels could be utilized as a matrix for enzyme entrapment, 100 μL of a 10 mg/50 mL solution of the α-amylase enzyme was added to the hydrogel of compound 10. The hydrogel was made by dissolving 25 mg of compound 10 in 1.90 mL of phosphate buffered saline (PBS) afterwards, 100 μL (0.1 mL) of the enzyme solution was added and the vial was allowed to
further cool for gel formation. The gel was used immediately for the experiment. The substrate solution was made up of 1 mL PBS and 1 mL of the starch solution which was 0.50 g in 100 mL of deionized (DI) water. The substrate solution was placed on top of the gel and allowed to sit at 26 °C (without shaking) for different time points (2h, 4h, 6h, 8h). Fresh substrate solution was placed on top of the gel for each time point.

Since maltose cannot be quantified directly, an established protocol for quantifying reducing sugars using dinitrosalicylic acid (DNS) was adopted. After the specific time passed, 1 mL of the color reagent (DNS) was added to the solution and it was placed in boiling water for 15 minutes. After boiling, the tubes were allowed to cool in an ice bath and then diluted, later the absorbance readings were taken at 540 nm. A calibration curve was made initially using different concentrations of maltose to calculate the molar extinction coefficient which was found to be 1467.1 cm⁻¹ M⁻¹. As you can see from figure 66, the enzyme retained its activity overtime and was in fact able to produce maltose from starch. The concentration of maltose increased overtime however, there seem to be a lag in the activity over the first 2 h at the beginning of the experiment. The enzyme was possibly denatured initially because the temperature at which it was introduced in the gel solution was too high. However, it is clear from the observed activity after 2 h that the enzyme was able to refold and regain its activity. A similar situation was also seen previously in an experiment where trypsin and α-amylase adsorbed on titanium dioxide nanoparticles, were able to regain their activity after being inactivated at high temperatures.

As you can see from the gel photos in figure 67; the gel retained its stability overtime but started to degrade during the 8 h experiment. With that, the assay will be repeated with a higher gelation
concentration and also other gelators will be utilized to see if stability can be increased and improve
the chances of having recyclable gels for enzymatic catalysis. Also, in order to reduce the lag time;
the experiment will be carried out at least 2 h or more after the gel is made. This will allow for the
enzyme to regain its activity in case the temperature at which it was added was too high to cause
any form of denaturation. For future studies, it would be important to investigate possible leaching
of the enzyme into the solution phase to identify its impact on increased enzyme activity at any
given time point. In addition to that, several experiments could be done to detect the optimal
inoculation temperature at which the enzyme has maximum activity. This would be useful to
remove the delay time seen in the reported experiment.

Figure 66. Quantified results of maltose produced by the α-amylase entrapped within the hydrogel
of compound 10 using absorbance at 540 nm and the molar extinction coefficient which was found
to be 1467.1 cm\(^{-1}\) M\(^{-1}\).
Figure 67. Images of the enzyme entrapped hydrogel at 0 h before addition of the substrate solution and 8 h with the substrate solution.

3.2.5 SALT-BASED GELATORS

With the effective gelator 21 in hand, we then explored the formation of various complexes with different carboxylic acids as shown in scheme 9. The gelation ability of the amine salts were tested in water, DMSO:H₂O (v/v 1:2) and EtOH/H₂O (v/v 1:3). They formed gels at relatively higher concentrations in comparison to compound 21 and the results are summarized in table 7. The benzoate 26 formed gels in DMSO:H₂O (v/v 1:2) at 5.0 mg/mL and in water at 20.0 mg/mL. The salt 24 and 25 also formed gels in DMSO:H₂O (v v 1:2) at 20.0 mg/mL. The coumarin salt 24 was the only one to form a gel in EtOH:H₂O (v/v 1:3) at 10.0 mg/mL.

Table 7. Gelation test results of compounds 24-26.

<table>
<thead>
<tr>
<th>Cpd. #</th>
<th>EtOH: H₂O (1:3)</th>
<th>DMSO: H₂O (1:2)</th>
<th>H₂O</th>
</tr>
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<tr>
<td>24</td>
<td>G10.0o</td>
<td>G20.0o</td>
<td>P</td>
</tr>
<tr>
<td>25</td>
<td>P</td>
<td>G20.0o</td>
<td>P</td>
</tr>
<tr>
<td>26</td>
<td>PS</td>
<td>G5.0o</td>
<td>G20.0o</td>
</tr>
</tbody>
</table>

A few gel photos are shown in figure 68 and the optical micrographs of several dried gels are shown in figure 69. The coumarin acid complex formed curved tubules, the gels of the pyrene complex 25 and benzoate 26 both formed uniform fibrous assemblies. All the salt-based gels depicted the typical fibrous morphology that is generally seen.
Figure 68. Gel photos of compounds 21, 24 and 26. a) Opaque gel of compound 21 in DMSO:H₂O (v/v 1:2) at 2.86 mg/mL; b) Opaque gel of compound 24 in EtOH:H₂O (v/v 1:3) at 10 mg/mL; c) Opaque gel of compound 26 in DMSO:H₂O (v/v 1:2) at 5 mg/mL.

Figure 69. Optical micrographs of the dried gels under brightfield. a) Gel of compound 21 with coumarin-3-carboxylic acid (1:1 mole ratio) in DMSO:H₂O (v/v 1:2) at 7.0 mg/mL; b) Gel of complex 25, 6.7 mg/mL in DMSO:H₂O (v1:2); c) Gel of complex 26, 4 mg/mL in DMSO:H₂O (v1:2).
The amine salts 24 and 25 both showed strong UV absorbance and fluorescence. The gel photos and the representative fluorescence intensities are portrayed in figures 70 and 71. The gels of the amine salts 24 and 25 were opaque in appearance but had strong fluorescent intensities in ethanol at low concentrations. This shows that attaching different chromophores in the design of supramolecular gelators can yield gels that fluoresce which could be studied further for the potential applications as chemosensors or in molecular recognition.233, 234

Figure 70. Gel photos of the amine salts. a/b) Compound 24 (2 mg in 0.1 mL EtOH and 0.2 mL H2O) before and under UV light. c/d) Compound 25 (2 mg in 0.1 mL DMSO and 0.2 mL H2O) before and under UV light. UV-Light (302 nm).
Figure 71. The fluorescence intensity spectra of the amine salts. Concentration of compound 24: $2.523 \times 10^{-5}$ mol/L, Concentration compound 25: $1.721 \times 10^{-5}$ mol/L.

All the compounds were characterized using $^1$H NMR, $^{13}$C NMR, LC-MS, FT-IR and melting point. The $^1$H NMR, $^{13}$C NMR and FT-IR spectra of some selected compounds are shown in the end of the chapter figures 72-77.
Figure 72. $^1$H and $^{13}$C NMR spectra of compound 10.
Figure 73. $^1$H and $^{13}$C NMR spectra of compound 15.
Figure 74. $^1$H and $^{13}$C NMR spectra of compound 21.
Figure 75. FT-IR spectra of compound 10.

Figure 76. FT-IR spectra of compound 21.
3.3 CONCLUSIONS

In summary, I have synthesized and characterized a small library of ethers, esters, amines and their salts. The ether and ester derivatives were able to function as effective low molecular weight gelators, with most having a fibrous morphology. The aniline derivative from the amines and the propionic acid derivative from the esters were the most efficient gelators. Many of the amines that were studied did not form gels in aqueous solutions or organic solvents. The aniline derivative was selected to form amine salts with carboxylic acids, and they were also gelators in aqueous solutions with fluorescent properties. The drug release studies demonstrate that the propionic ester derivative 10 was able to entrap and enable the slow and steady release of hydroxychloroquine from the gel matrix. It was also able to entrap alpha amylase with retention of its activity. Future studies could include the exploration of different acids for salt formation and gelation, other important enzymes

Figure 77. FT-IR spectra of compound 25.
could be immobilized, and the amine salts could be tested for electrical conductivity and investigated for potential applications.

3.4 EXPERIMENTAL SECTION

General method and materials: Reagents and solvents were used as they were received from the suppliers. All purification was conducted by flash column chromatography using 230-400 mesh silica gel obtained from Natland International Corporation, unless otherwise noted. Deacetylation reaction was performed in a Mars 6 microwave reactor from CEM Corporation. NMR analysis was conducted using a 400 MHz Bruker NMR spectrometer. Melting point measurements were carried out using a Fisher-Johns Melting Point apparatus. UV-Vis experiments were done using a SHIMADZU UV-1800 Spectrophotometer.

Optical Microscopy: A thin slice of the gel was transferred onto a clean glass slide and then left to air dry for a day or so. The gel was then observed under an Olympus BX60M optical microscope at brightfield using an Olympus DP73-1-51 high-performance 17 MP digital camera with pixel shifting and Peltier cooling. The program used to acquire and store the images is CellSens Dimension 1.11.

Gel Testing: Approximately 2 mg of the desired compound was placed in a one-dram vial and 0.1 mL of the gelation solvent or solution was transferred inside the vial to attain a concentration of 20 mg/mL. The vial was then heated until the gelator dissolved fully; sometimes, the mixture was sonicated to help with dissolving the compound and the mixture was left to cool for approximately 15 min or longer for the gel to form. After this period, if the solution was clear, this was recorded
as soluble; if the solid reappeared, this was recorded as a precipitate; if the sample formed a gel, then the vial was inverted; if no solvent was flowing, this indicated that a stable gel was formed; otherwise, this was recorded as unstable gel. If gelation occurs, another 0.1 mL is added, and the method is repeated until an unstable gel is formed. The minimum gelation concentration (MGC), the concentration prior to unstable gelation, was recorded.

**Hydroxychloroquine Release Studies:** 20 mL of a $2.8805 \times 10^{-5}$ mol/L solution of hydroxychloroquine was made by dilution from a stock solution containing 5 mg in 50 mL. 2 mL of the diluted solution was used to make the gel of compound 10 (0.02 g in 2 mL). The gel was made by heating then cooling and was allowed to sit for 50 minutes before PBS (2 mL, pH 7-7.4) was added on top. The gel was placed in an incubator at 37 °C and the absorption was checked at different time points (200-600 nm). Absorbance was taken with a SHIMADZU UV-1800 Spectrophotometer.

**Enzyme Entrapment and Activity Measurements:** The enzyme solution was made by dissolving 10 mg in 50 mL of DI water. The starch solution was made by dissolving 0.5003 g in 100 mL DI water. The hydrogel was made by dissolving 25 mg of compound 10 in a scintillation vial in 1.90 mL of PBS in the presence of heat. After short cooling, 100 μL (0.1mL) of the enzyme solution was added and the vial allowed to further cool for gel formation. The gel was used immediately. The substrate solution for the α-amylase enzyme consisted of 1 mL of the starch solution and 1 mL of phosphate buffer pH 7-7.4. The substrate solution (total 2 mL) was placed on top of the gel and allowed to sit at 26 °C (NO shaking) for different time points (2 h, 4 h, 6 h, 8 h). Fresh substrate solution was placed on top of the gel for each time point. After the specific
time passed, 1 mL color reagent (dinitrosalicylic acid) was added to the solution and it was placed in boiling water for 15 minutes. After the 15 minutes in the boiling water the tubes were cooled under running water then placed in an ice bath to cool to room temperature. The absorbance of the solution was then taken at 540 nm. The concentration of maltose present was calculated based on the extinction coefficient from the standard curve.

Synthesis of the 4,6-Benzyl protected headgroup 7

Compound 5 (0.2649 g, 1 equiv, 0.94 mmol) was added to a 100 mL round bottom flask along with 8 mL of DCM (anhydrous), DIEA (0.25 mL, 1.5 equiv) and potassium carbonate (0.3905 g, 3 equiv, 2.83 mmol). This mixture was stirred at 0 °C for approximately 30 minutes, during this time 6-bromohexanoyl chloride (1.2 equiv) was diluted with DCM (anhydrous). Afterwards, it was added in a dropwise manner to the round bottom flask at 0 °C. The reaction mixture was then stirred for an additional 2.5 h from 0 °C to rt. After the starting material was fully consumed, the DCM was removed from the reaction mixture via the rotavap. Workup was done using DCM (15 mL x 3), 5% Sodium bicarbonate and then with water (10 mL). The combined organic layer was dried over Na₂SO₄ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 2.5% MeOH/DCM to afford a white solid 400.7 mg, 93%) as the desired product. (Rf = 0.43 in 3% MeOH/DCM). mp 190-192 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.55- 7.45 (m, 2H), 7.43-7.30 (m, 3H), 5.85 (d, J = 8.6 Hz, 1H), 5.57 (s, 1H), 4.73 (d, J = 3.8 Hz, 1H), 4.33-4.19 (m, 2H), 3.91 (t, J = 9.6 Hz, 1H), 3.84-3.73 (m, 2H), 3.59 (t, J = 9.0 Hz, 1H), 3.46-3.37 (m, 5H), 2.28 (t, J = 7.4 Hz, 2H), 1.93-1.83 (m, 2H), 1.75-1.65 (m, 2H), 1.54-1.45 (m, 2H); ¹³C (100MHz, CDCl₃) δ 174.1, 137.1, 129.2, 128.3, 126.3, 102.0, 98.8, 82.1,
General Procedure for the ester derivatives 10-14 synthesis from headgroup 7

Compound 7 will be added to a 50 mL round bottom flask. The respective carboxylic acids, followed by DIEA and potassium carbonate will then be added to the flask and the reaction mixture will be allowed to stir in DMF for 6-8 h at 75 °C. After the 6-8 h, TLC and ¹H-NMR will be used to check if the reaction is finished. After the starting material is fully consumed DMF will be removed from the reaction mixture via the rotavap or by drying under air. Workup will be done using DCM, cold NaHCO₃ solution (5%) and then with water. The combined organic layer will be dried over Na₂SO₄ (anhydrous), filtered and concentrated to give the crude, which will be purified by column chromatography.

Synthesis of ester derivative 10

Compound 7 (0.1305 g, 0.28 mmol, 1 equiv) was added to a 50 mL round bottom flask. Propionic acid (0.0258 g, 0.35 mmol, 1.2 equiv) followed by DIEA (0.050 mL, 0.29 mmol, 1 equiv) and potassium carbonate (0.0416 g, 0.30 mmol, 1 equiv) were then added to the flask. The reaction mixture was allowed to stir in 3 mL of DMF for 6 h at 70 °C. After the 6 h, TLC and ¹H-NMR confirmed the starting material was fully consumed. DMF was removed from the reaction mixture by drying under air. Workup was done using DCM (15 mL x 3)/ cold NaHCO₃ (5% aq, 5 mL) and then with water. The combined organic layer was dried over Na₂SO₄ (anhydrous), filtered and concentrated to give the pure compound in the form of a white solid (121.7 mg, 95%) as the desired product. (Rᶠ = 0.44 in 5% MeOH/DCM). mp 154 -156 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.54-
7.46 (m, 2H), 7.42-7.32 (m, 3H), 5.83 (d, J = 8.5 Hz, 1H), 5.57 (s, 1H), 4.73 (d, J = 3.8 Hz, 1H), 4.33-4.20 (m, 2H), 4.07 (t, J = 6.5 Hz, 2H), 3.91 (t, J = 9.6 Hz, 1H), 3.83-3.74 (m, 2H), 3.59 (t, J = 9.0 Hz, 1H), 3.41 (s, 3H), 2.37-2.23 (m, 4H), 1.75-1.62 (m, 4H) 1.46-1.35 (m, 2H), 1.13 (t, J = 7.6 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 174.6, 174.2, 137.1, 129.2, 128.3, 126.3, 101.9, 98.8, 82.1, 68.8, 64.1, 62.3, 55.3, 54.0, 36.4, 28.4, 27.6, 25.5, 25.1, 9.1. LC-MS m/z calcd. for C23H34NO8 [M + H] 452.22, found 452.3.

**Synthesis of ester derivative 11**

Compound 7 (0.0750 g, 0.16 mmol, 1 equiv) was added to a 50 mL round bottom flask. 4-methoxybenzoic acid (0.0299 g, 0.20 mmol, 1.2 equiv) followed by DIEA (0.029 mL, 1 equiv) and potassium carbonate (0.0463 g, 0.33 mmol, 2 equiv) were then added to the flask. The reaction mixture was allowed to stir in 3 mL of DMF for 8 h at 70 °C. After the 6 h, TLC and 1H-NMR confirmed the starting material was fully consumed. DMF was removed from the reaction mixture by drying under air. Workup was done using DCM (10 mL x 3)/ cold NaHCO3 (5% aq, 5 mL) and then with water. The combined organic layer was dried over Na2SO4 (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 2.0% MeOH/DCM to afford a white solid (80.4 mg, 93%) as the desired product. (Rf = 0.26 in 3% MeOH/DCM). mp 126 -128 °C. 1H NMR (400 MHz, CDCl3) δ 7.98 (d, J = 8.8, 2H ) 7.54- 7.45 (m, 2H), 7.41-7.31 (m, 3H), 6.91 (d, J = 8.9 Hz, 2H), 5.84 (d, J = 8.3, 1H), 5.57 (s, 1H), 4.72 (d, J = 3.8 Hz, 1H), 4.37-4.17 (m, 4H), 3.93-3.73 (m, 6H), 3.58 (t, J = 8.6 Hz, 1H), 3.39 (s, 3H), 2.34-2.24 (m, 2H), 1.83-1.69 (m, 4H) 1.54-1.45 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 174.2, 166.4, 163.3, 137.1, 131.5, 129.2, 128.3, 126.3, 122.8, 113.6, 101.9, 98.8, 82.1,
70.9, 68.8, 64.4, 62.3, 55.4, 55.3, 54.0, 36.4, 28.6, 25.6, 25.2. LC-MS m/z calcd. for C_{28}H_{36}NO_{9} [M + H] 530.23, found 530.2

**Synthesis of ester derivative 12**

Compound 7 (0.1018 g, 0.22 mmol, 1 equiv) was added to a 50 mL round bottom flask. Nitrobenzoic acid (0.0467 g, 0.28 mmol, 1.2 equiv) followed by DIEA (0.038 mL, 1 equiv) and potassium carbonate (0.0687 g, 0.50 mmol, 2 equiv) were then added to the flask. The reaction mixture was allowed to stir in 5 mL of DMF for 5.5 h at 70 °C. After the 5.5 h, TLC and $^1$H-NMR confirmed the starting material was fully consumed. DMF was removed from the reaction mixture by drying under air. Workup was done using DCM (15 mL x 3)/ cold NaHCO$_3$ (5% aq, 5 mL) and then with water. The combined organic layer was dried over Na$_2$SO$_4$ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 20% EtOAc/Hex followed by 0.5% MeOH/DCM with an increase in the methanol concentration until the product came off the column. A white solid (98.5 mg, 82%) was obtained as the desired product. ($R_f = 0.60$ in 5% MeOH/DCM). mp 164 -166 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.28 (d, $J = 8.8$ Hz, 2H), 8.20 (d, $J = 8.8$ Hz, 2H), 7.52-7.47 (m, 2H), 7.39-7.33 (m, 3H), 5.82 (d, $J = 8.5$ Hz, 1H), 5.57 (s, 1H), 4.72 (d, $J = 3.8$ Hz, 1H), 4.37 (t, $J = 6.6$ Hz, 2H), 4.30-4.20 (m, 2H), 3.90 (t, $J = 9.6$ Hz, 1H), 3.82-3.75 (m, 2H), 3.58 (t, $J = 8.7$ Hz, 1H), 3.40 (s, 3H), 2.30 (t, $J = 7.4$ Hz, 2H), 1.87-1.67 (m, 4H), 1.56-1.46 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.0, 164.7, 150.5, 137.1, 135.7, 130.7, 129.2, 128.3, 126.3, 123.5, 102.0, 98.8, 82.1, 70.9, 68.8, 65.7, 62.4, 55.3, 54.0, 36.3, 28.4, 25.5, 25.1. LC-MS m/z calcd. for C$_{27}$H$_{33}$N$_2$O$_{10}$ [M + H] 545.21, found 545.2.
Synthesis of ester derivative 13

Compound 7 (0.1206 g, 0.26 mmol, 1 equiv) was added to a 50 mL round bottom flask. Benzoic acid (0.0429 g, 0.35 mmol, 1.2 equiv) followed by DIEA (0.045 mL, 1 equiv) and potassium carbonate (0.0846 g, 0.61 mmol, 2 equiv) were then added to the flask. The reaction mixture was allowed to stir in 5 mL of DMF for 8 h at 70 °C. After the 8 h, TLC and $^1$H-NMR confirmed the starting material was fully consumed. DMF was removed from the reaction mixture by drying under air. Workup was done using DCM (15 mL x 3)/ cold NaHCO$_3$ (5% aq, 5 mL) and then with water. The combined organic layer was dried over Na$_2$SO$_4$ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure 50% EtOAc/Hexane then continuing with 0.5-2.5% MeOH/DCM to afford a white solid (107.3 mg, 82%) as the desired product. (R$_f$ = 0.37 in 5% MeOH/DCM). mp 150-152 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.08–7.99 (m, 2H), 7.56–7.48 (m, 3H), 7.46–7.40 (m, 2H), 7.40–7.33 (m, 3H), 5.84 (d, $J$ = 8.6 Hz, 1H), 5.57 (s, 1H), 4.72 (d, $J$ = 3.8 Hz, 1H), 4.34–4.20 (m, 4H), 3.89 (t, $J$ = 9.6 Hz, 1H), 3.82–3.74 (m, 2H), 3.58 (t, $J$ = 9.0 Hz, 1H), 3.39 (s, 3H), 2.29 (t, $J$ = 7.4, 2H), 1.84–1.69 (m, 4H), 1.55–1.45 (m, 2H);$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.2, 166.6, 137.1, 132.8, 130.4, 129.5, 129.1, 128.3, 128.2, 126.3, 101.9, 98.8, 82.1, 70.7, 68.8, 64.7, 62.3, 55.3, 54.1, 36.4, 28.5, 25.6, 25.2. LC-MS m/z calcd. for C$_{27}$H$_{34}$NO$_8$ [M + H] 500.22, found 500.

Synthesis of ester derivative 14

Compound 7 (0.1025 g, 0.22 mmol, 1 equiv) was added to a 50 mL round bottom flask, followed by DIEA (0.038 mL, 1 equiv), potassium carbonate (0.0698 g, 0.51 mmol, 2 equiv) and bromo-benzoic acid (0.0543 g, 0.27 mmol, 1.2 equiv) were then added to the flask. The reaction was allowed to stir in 4 mL of anhydrous DMF for 6 h at 75 °C. After the 6 h, TLC and $^1$H-NMR
confirmed the starting material was fully consumed. DMF was removed from the reaction mixture by drying under air. Workup was done using DCM (10 mL x 3)/ NaHCO₃ (5% aq, 5 mL) and then with water (5 mL). The combined organic layer was dried over Na₂SO₄ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 2.5% MeOH/DCM to afford a white solid (120.6 mg, 93%) as the desired product. (Rₚ = 0.34 in 3% MeOH/DCM). mp 166-168 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.53-7.47 (m, 2H), 7.41-7.32 (m, 3H), 5.84 (d, J = 8.5 Hz, 1H), 5.57 (s, 1H), 4.72 (d, J = 3.8 Hz, 1H), 4.36-4.18 (m, 4H), 3.90 (t, J = 9.6 Hz, 1H), 3.84-3.73 (m, 2H), 3.59 (t, J = 8.9 Hz, 1H), 3.40 (s, 3H), 2.29 (t, J = 7.4 Hz, 2H), 1.84-1.70 (m, 4H), 1.54-.144 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 174.1, 165.9, 137.1, 131.7, 131.1, 129.3, 129.2, 128.3, 128.0, 126.3, 101.9, 98.8, 82.1, 70.8, 68.8, 65.0, 62.4, 55.3, 54.1, 36.4, 28.5, 25.6, 25.1. LC-MS m/z calcd. for C₂₇H₃₃BrNO₈ [M + H] 578.13, found 578.

**Synthesis of ether derivative 15**

Compound 7 (0.1008 g, 0.22 mmol, 1 equiv) was added to a 50 mL round bottom flask. DIEA (0.038 mL, 1 equiv) followed by potassium carbonate (0.0617 g, 0.45 mmol, 2 equiv) and 4-methoxyphenol (0.0549 g, 0.44 mmol, 2 equiv) were then added to the flask. The reaction mixture was allowed to stir in 5 mL of DMF for 6 h at 70 °C. After the 6 h, TLC and ¹H-NMR confirmed the starting material was fully consumed. DMF was removed from the reaction mixture by drying under air. Workup was done using DCM (15 mL x 3)/ cold NaHCO₃ (5% aq, 5 mL) and then with cold water. The combined organic layer was dried over Na₂SO₄ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 2.0% MeOH/DCM to afford a white solid (85.8 mg, 78%) as the desired product.
(Rf = 0.43 in 5% MeOH/DCM). mp 164-166 °C. 1H NMR (400 MHz, CDCl3) δ 7.53- 7.46 (m, 2H), 7.41-7.32 (m, 3H), 6.81 (s, 4H), 5.84 (d, J = 8.6 Hz, 1H), 5.57 (s, 1H), 4.72 (d, J = 3.8 Hz, 1H), 4.35-4.19 (m, 2H), 3.95-3.87 (m, 3H), 3.83-3.74 (m, 5H), 3.59 (t, J = 9.0 Hz, 1H), 3.40 (s, 3H), 2.29 (t, J = 7.5 Hz, 2H), 1.83-1.70 (m, 4H) 1.57-1.48 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 174.3, 153.8, 153.2, 137.1, 129.2, 128.3, 126.3, 115.4, 114.7, 101.9, 98.8, 82.1, 70.9, 68.9, 68.3, 62.3, 55.8, 55.3, 54.0, 36.5, 29.1, 25.7, 25.3. LC-MS m/z calcd. for C27H36NO8 [M + H] 502.24, found 502.

Synthesis of ether derivative 16

Compound 7 (0.1010 g, 0.22 mmol, 1 equiv) was added to a 50 mL round bottom flask. DIEA (0.038 mL, 1 equiv) followed by potassium carbonate (0.0677 g, 0.49 mmol, 2 equiv) and 4-nitrophenol (0.0613 g, 0.44 mmol, 2 equiv) were then added to the flask. The reaction mixture was allowed to stir in 4 mL of DMF for 6 h at 70 °C. After the 6 h, TLC and 1H-NMR confirmed the starting material was fully consumed. DMF was removed from the reaction mixture by drying under air. Workup was done using DCM (15 mL x 3)/ cold NaHCO3 (5% aq, 5 mL) and then with cold water. The combined organic layer was dried over Na2SO4 (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 1.5% MeOH/DCM to afford a white solid (99.9 mg, 88%) as the desired product. (Rf = 0.39 in 5% MeOH/DCM). mp 205-207 °C. 1H NMR (400 MHz, CDCl3) δ 8.18 (d, J = 8.9 Hz, 2H), 7.55- 7.45 (m, 2H), 7.44-7.30 (m, 3H), 6.93 (d, J = 9.1Hz, 2H), 5.83 (d, J = 8.5 Hz, 1H), 5.57 (s, 1H), 4.72 (d, J = 3.8 Hz, 1H), 4.35-4.19 (m, 2H), 4.05 (t, J = 6.3 Hz, 2H), 3.90 (t, J = 9.6 Hz, 1H), 3.84-3.73 (m, 2H), 3.59 (t, J = 8.8 Hz, 1H), 3.40 (s, 3H), 2.30 (t, J = 7.4 Hz, 2H), 1.90-1.69 (m, 4H), 1.58-1.49 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 174.1, 164.1, 141.5, 137.1, 129.2,
Synthesis of ether derivative 17

Compound 7 (0.1126 g, 0.25 mmol, 1 equiv) was added to a 50 mL round bottom flask. DIEA (0.042 mL, 1 equiv) followed by potassium carbonate (0.0681 g, 0.49 mmol, 2 equiv) and phenol (0.0468 g, 0.49 mmol, 2 equiv) were then added to the flask. The reaction mixture was allowed to stir in 5 mL of DMF for 7 h at 70 °C. After the 7 h, TLC and $^1$H-NMR confirmed the starting material was fully consumed. DMF was removed from the reaction mixture by drying under air. Workup was done using DCM (15 mL x 3)/ cold NaHCO$_3$ (5% aq, 5 mL) and then with cold water. The combined organic layer was dried over Na$_2$SO$_4$ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 2% MeOH/DCM to afford a white solid (102.1 mg, 88%) as the desired product. ($R_f = 0.69$ in 5% MeOH/DCM). mp 147-149 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.54-7.46 (m, 2H), 7.40-7.33 (m, 3H), 7.29-7.24 (m, 2H), 6.99-6.83 (m, 3H), 5.85 (d, $J = 8.7$ Hz, 1H), 5.57 (s, 1H), 4.72 (d, $J = 3.8$ Hz, 1H), 4.32-4.20 (m, 2H), 3.99-3.87 (m, 3H), 3.83-3.74 (m, 2H), 3.59 (t, $J = 9.0$ Hz, 1H), 3.40 (s, 3H), 2.29 (t, $J = 7.5$ Hz, 2H), 1.85-1.69 (m, 4H), 1.57-1.49 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.3, 159.0, 137.2, 129.4, 129.2, 128.9, 126.3, 120.6, 114.5, 101.9, 98.8, 82.0, 70.7, 68.8, 67.5, 62.4, 55.3, 54.1, 36.5, 29.0, 25.7, 25.3. LC-MS m/z calcd. for C$_{26}$H$_{34}$NO$_7$ [M + H] 472.23, found 472.2.
Synthesis of ether derivative 18

Compound 7 (0.1035 g, 0.23 mmol, 1 equiv) was added to a 50 mL round bottom flask. DIEA (0.039 mL, 1 equiv) followed by potassium carbonate (0.0696 g, 0.50 mmol, 2 equiv) and 4-bromophenol (0.0781 g, 0.45 mmol, 2 equiv) were then added to the flask. The reaction mixture was allowed to stir in 4 mL of DMF for 7 h at 75 °C. After the 7 h, TLC and ¹H-NMR confirmed the starting material was fully consumed. DMF was removed from the reaction mixture by drying under air. Workup was done using DCM (15 mL x 3)/ cold NaHCO₃ (5% aq, 5 mL) and then with cold water. The combined organic layer was dried over Na₂SO₄ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 3% MeOH/DCM to afford a white solid (96.9 mg, 78%) as the desired product. (R_f = 0.34 in 5% MeOH/DCM). mp 187-189 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.52-7.47 (m, 2H), 7.41-7.31 (m, 5H), 6.79-6.72 (m, 2H), 5.84 (d, J = 8.5 Hz, 1H), 5.57 (s, 1H), 4.73 (d, J = 3.9 Hz, 1H), 4.33-4.20 (m, 2H), 3.95-3.87 (m, 3H), 3.83-3.75 (m, 2H), 3.59 (t, J = 9.0 Hz, 1H), 3.40 (s, 3H), 3.58 (t, J = 9.0 Hz, 1H), 3.40 (s, 3H), 2.29 (t, J = 7.4 Hz, 2H), 1.84-1.70 (m, 4H), 1.57-1.47 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 174.3, 158.1, 137.1, 132.2, 129.2, 128.3, 126.3, 116.3, 112.7, 102.0, 98.8, 82.1, 70.9, 68.8, 67.9, 62.4, 55.3, 54.1, 36.5, 28.9, 25.6, 25.2. LC-MS m/z calcd. for C₂₆H₃₃BrNO₇ [M + H] 550.14, found 550.1.

Synthesis of amine derivative 19

Compound 7 (0.0501 g, 0.11 mmol, 1 equiv) was added to a 50 mL round bottom flask along with ethylamine (1 mL, 17.7 mmol, 160.5 equiv.). The reaction mixture was allowed to stir in 0.3 mL of DMF for 12 h at rt. After the 12 h, TLC and ¹H-NMR confirmed the starting material was fully consumed. DMF was removed from the reaction mixture by drying under air. Workup was done
using DCM (25 mL x 3) and water (15 mL). The combined organic layer was dried over Na$_2$SO$_4$ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 20% MeOH/DCM to afford a white solid (432.0 mg, 94%) as the desired product. (R$_f$ = 0.37 in 10% MeOH/DCM). mp 171-173 °C. $^1$H NMR δ 7.53-7.43 (m, 2H), 7.39-7.29 (m, 3H), 6.81 (d, $J = 8.6$ Hz, 1H), 5.53 (s, 1H), 4.71 (d, $J = 3.5$ Hz, 1H), 4.30-4.21 (m, 1H), 4.20-4.11 (m, 1H), 3.99 (t, $J = 9.7$ Hz, 1H), 3.85-3.70 (m, 2H), 3.59 (t, $J = 9.1$ Hz, 1H), 3.38 (s, 3H), 3.00-2.77 (m, 4H), 1.93-1.71 (m, 4H), 1.64-1.51 (m, 2H), 1.42-1.33 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 137.2, 129.2, 128.2, 126.4, 102.0, 99.1, 81.8, 69.2, 68.9, 62.7, 55.3, 54.3, 54.2, 46.9, 46.8, 43.1, 43.0, 35.2, 25.1, 24.9, 23.7, 11.1. LC-MS m/z calcd. for C$_{22}$H$_{35}$N$_2$O$_6$ [M + H] 423.24, found 423.2.

**Synthesis of amine derivative 20**

Compound 7 (0.0506 g, 0.11 mmol, 1 equiv) was added to a 50 mL round bottom flask along with propylamine (1 mL, 12.2 mmol, 110.6 equiv.). The reaction mixture was allowed to stir in 0.2 mL of DMF for 10 h at rt. After the 10 h, TLC and $^1$H-NMR confirmed the starting material was fully consumed. DMF was removed from the reaction mixture by drying under air. Workup was done using DCM (25 mL x 3) and water (15 mL). The combined organic layer was dried over Na$_2$SO$_4$ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 20% MeOH/DCM to afford a white solid (473.0 mg, 98%) as the desired product. (R$_f$ = 0.6 in 10% MeOH/DCM). mp 187-189 °C. $^1$H NMR δ 7.51-7.43 (m, 2H), 7.38-7.28 (m, 3H), 6.93 (d, $J = 8.7$ Hz, 1H), 5.52 (s, 1H), 4.70 (d, $J = 3.5$ Hz, 1H), 4.28-4.19 (m, 1H), 4.18-4.10 (m, 1H), 3.96 (t, $J = 9.7$ Hz, 1H), 3.84-3.69 (m, 2H), 3.55 (t, $J = 9.1$ Hz, 1H), 3.37 (s, 3H), 2.92-2.76 (m, 4H), 2.35-2.25 (m, 2H), 1.82-1.72 (m, 4H), 1.64-1.50
(m, 2H), 1.46-1.36 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 137.2, 129.1, 128.2, 126.3, 101.9, 99.1, 81.9, 69.1, 68.9, 62.7, 55.3, 54.0, 47.4, 35.1, 25.1, 24.8, 23.7, 19.2, 11.0

LC-MS m/z calcd. for C$_{23}$H$_{37}$N$_2$O$_6$ [M + H] 437.26, found 437.

**Synthesis of amine derivative 21**

Compound 7 (0.0754 g, 0.16 mmol, 1 equiv) was added to a 50 mL round bottom flask along with aniline (3 mL, 11.0 mmol, 68.8 equiv.). The reaction mixture was allowed to stir for 8 h at 70 °C. After the 8 h, TLC and $^1$H-NMR confirmed the starting material was fully consumed. The aniline was removed by drying under air. Workup was done using DCM and 0.1 N HCl, the DCM layer was then treated with saturated sodium bicarbonate solution and water. The combined organic layer was dried over Na$_2$SO$_4$ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 3% MeOH/DCM to afford a white solid (56.8 mg, 73%) as the desired product. (R$_f$ = 0.43 in 5% MeOH/DCM). mp 178-180 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.52-7.48 (m, 2H), 7.38-7.34 (m, 3H), 7.20-7.13 (m, 2H), 6.71 (t, J = 7.3 Hz, 1H), 6.63 (d, J = 7.6 Hz, 2H), 5.87 (d, J = 8.6 Hz, 1H), 5.56 (s, 1H), 4.72 (d, J = 3.8 Hz, 1H), 4.30-4.20 (m, 2H), 3.90 (t, J = 9.6 Hz, 1H), 3.82-3.74 (m, 2H), 3.58 (t, J = 9.0 Hz, 1H), 3.39 (s, 3H), 3.12 (t, J = 7.0 Hz, 2H), 2.27 (t, J = 7.4 Hz, 2H), 1.78-1.59 (m, 4H), 1.50-1.41 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 174.3, 147.9, 137.1, 129.3, 129.2, 128.3, 126.3, 117.7, 113.2, 101.9, 98.8, 82.1, 70.8, 68.8, 62.4, 55.3, 54.0, 44.0, 36.4, 29.0, 26.5, 25.2. LC-MS m/z calcd. for C$_{26}$H$_{35}$N$_2$O$_6$ [M + H] 471.24, found 471.
Synthesis of amine derivative 22

Compound 7 (0.0762 g, 0.17 mmol, 1 equiv) was added to a 50 mL round bottom flask. Imidazole (0.0339 g, 3 equiv, 0.50 mmol) and potassium carbonate (0.0510 g, 0.37 mmol, 2 equiv) were then added to the flask. The reaction mixture was allowed to stir in 2 mL of DMF for 12 h at 70 °C. After the 12 h, TLC and ¹H-NMR confirmed the starting material was fully consumed. DMF was removed from the reaction mixture via by drying under air. Workup was done using DCM and water. The combined organic layer was dried over Na₂SO₄ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 3% MeOH/DCM to afford a white solid (46.6 mg, 63%) as the desired product. (Rᵣ = 0.3 in 10% MeOH/DCM). mp 169-171 °C. ¹H NMR δ 7.91 (bs, 1H), 7.53-7.46 (m, 2H), 7.39-7.32 (m, 3H), 7.06 (bs, 1H), 6.86, (bs, 1H), 6.10 (d, J = 8.3 Hz, 1H), 5.57 (s, 1H), 4.75 (d, J = 3.7 Hz, 1H), 4.31-4.24 (m, 1H), 4.21-4.12 (m, 1H), 3.98-3.85 (m, 3H), 3.83-3.74 (m, 2H), 3.62 (t, J = 9.1 Hz, 1H), 3.39 (s, 3H), 2.24 (t, J =7.1 Hz, 2H), 1.82-1.60 (m, 4H), 1.37-1.25 (m, 2H);¹³C NMR (100 MHz, CDCl₃) δ 173.8, 137.2, 129.2, 128.8, 128.3, 126.3, 118.9, 102.0, 98.8, 82.1, 70.4, 68.9, 62.4, 55.3, 54.2, 46.9, 36.1, 30.6, 25.8, 24.7. LC-MS m/z calcd. for C₂₃H₃₂N₃O₆ [M + H] 446.22, found 446.

Synthesis of amine derivative 23

Compound 7 (0.0548 g, 0.12 mmol, 1 equiv) was added to a 50 mL round bottom flask along with pyridine (5 mL, 12.2 mmol, 110.6 equiv.). The reaction mixture was was allowed to stir at 70 °C for 6.5 h. After the 10 h, TLC and ¹H-NMR confirmed the starting material was fully consumed. After this, the pyridine was removed by drying under air to afford a white solid (604.0 mg, 94%) as the desired product. mp ~ 168 to 186 °C. ¹H NMR δ 8.9 (d, J = 5.6 Hz, 2H), 8.61 (t, J = 7.9 Hz, 1H), 8.14 (d, J = 7.1 Hz, 2H), 7.67-7.61 (m, 2H), 7.60-7.51 (m, 3H), 5.85 (s, 1H), 4.89-4.84 (m,
4H), expected doublet at the anomeric position is hiding under the D₂O peak, 4.68 (t, J = 7.4 Hz, 2H), 4.42 (d, J = 10.9 Hz, 1H), 4.39 (d, J = 10.9 Hz, 1H), 4.20-4.12 (m, 1H), 4.05-3.95 (m, 3H), 3.89-3.79 (m, 1H), 3.48 (s, 3H), 2.39 (t, J = 7.3 Hz, 1H), 2.18-2.06 (m, 2H), 1.80-1.67 (m, 2H), 1.51-1.39 (m, 2H); ¹³C NMR (100 MHz, D₂O) δ 179.5, 148.2, 146.7, 138.7, 132.5, 131.3, 130.8, 128.8, 104.5, 101.5, 83.6, 70.7, 65.1, 64.2, 58.0, 56.5, 37.8, 32.7, 27.2, 27.1. LC-MS m/z calcd. for C₂₅H₃₄N₂O₆⁺ Br⁻ [M + H] 458.23, found 458.

**Synthesis of amine salt 24**

Compound 21 (0.0199 g, 0.042 mmol, 1 equiv) was added to a 20 mL scintillation vial along with coumarin-3-carboxylic acid (0.0080 g, 0.042 mmol, 1 equiv.) and then 1.0 mL of methanol. The reaction mixture was allowed to stir for 5.5 h at rt. After this the compound was dried under reduced pressure on the rotavap and then vacuum pump to afford a white solid (262 mg, 94%) as the desired product.

**Synthesis of amine salt 25**

Compound 21 (0.0176 g, 0.037 mmol, 1 equiv) was added to a 20 mL scintillation vial along with 1-pyrenebutyric acid (0.0113 g, 0.037 mmol, 1 equiv.) and then 1.0 mL of methanol. The reaction mixture was allowed to stir for 5.5 h at rt. After this the compound was dried under reduced pressure on the rotavap and then vacuum pump to afford a white solid (283 mg, 98%) as the desired product.
Synthesis of amine salt 26

Compound 21 (0.0123 g, 0.026 mmol, 1 equiv) was added to a 20 mL scintillation vial along with benzoic acid (0.0033 g, 0.027 mmol, 1 equiv.) and then 1.0 mL of methanol. The reaction mixture was allowed to stir for 5.5 h at rt. After this the compound was dried under reduced pressure on the rotavap and then vacuum pump to afford a white solid (133 mg, 86%) as the desired product.

CHAPTER 4

THE DEVELOPMENT OF DIMERIC GLYCOLIPIDS AS SUPRAMOLECULAR GELATORS AND THEIR APPLICATIONS

PREFACE

This chapter is adapted from the following manuscript:


4.1 INTRODUCTION

One of the major pollutants in industry come from dyes; it has been reported that several hundred tons of this type of waste are produced yearly for the paper, textile and cosmetic industries with approximately 10-15% seeping into our water bodies.\textsuperscript{235, 236} The wastewater from the aforementioned industries contain several chemical dyes and other pollutants that are very harmful to the environment because they affect the entire cycle within the ecosystem.\textsuperscript{236} Both animals including humans and plants are affected, therefore finding new environmentally friendly solutions to treat wastewater remains a topic of interest in the scientific community.\textsuperscript{236, 237} Several methods that have been employed in this area include, bioremediation by the action of microbes, adsorption, oxidation-precipitation and coagulation.\textsuperscript{235-237} Decolorization through microbial degradation is only applicable on a large scale; whilst absorption has proven to be one the best ways to treat wastewater, the systems in place generate sludge afterwards which need to be disposed of and the process is quite costly.\textsuperscript{235, 236, 238} With this dire need, lots of researchers are studying supramolecular or low molecular weight gelators for environmental remediation.\textsuperscript{239-241}
Low molecular weight gelators derived from carbohydrates only require a small amount of the molecule for gel formation and form an interconnected network of fibers that support the bulk of the gel.\textsuperscript{12, 21, 63} The gels are generally formed by heating up the solutions and allowing them to cool.\textsuperscript{12} Supramolecular gels can be responsive to several stimuli such as light, heat, pH, metal ions, enzymes and others which allow for their exploitation in many systems.\textsuperscript{81, 242} Sugar-based molecules have been vastly studied and exploited for their gelation properties and immense applications in several fields.\textsuperscript{243} There are numerous characteristics that allow for carbohydrates to be molecules of high interest for driving research to solve many problems.\textsuperscript{69, 70, 81} They are easily accessible and renewable resources that are biocompatible, inexpensive and structurally diverse to enable modifications at different sites within the molecule.\textsuperscript{244}

Aside from the synthesis of modified monosaccharides and disaccharides, sugars have also been utilized for creating dimers, glycoclusters and dendrimers for use in materials science; a few representative structures are shown in figure 78.\textsuperscript{81, 245-249} Early research on glycoclusters or glycodendrimers focused on utilizing the click reaction for their generation with the presence of a triazole ring.\textsuperscript{250} Cyclodextrin as well as several amino acid derivatives have also been synthesized. Other naturally derived clusters that have been reported include those from cholesterol derivatives that have been studied for their notable gelation abilities with even thixotropic properties.\textsuperscript{251-253}
Glycoclusters and glycolipids have been utilized in the development of vaccines or carbohydrate-based drugs such as antibiotics that can assist with the problem of bacterial resistance.\textsuperscript{247-249} They serve as functionalized carbohydrates that can be utilized in many areas and hence their potential needs to be exploited. This chapter will focus on the investigation of glycolipids made from reacting di-carboxylic acids or diols with a glycolipid containing bromine as the leaving group. We have previously prepared monomeric esters and ethers that were excellent gelators with the potential to be utilized in biomedical applications and environmental remediation. Therefore, we hypothesized that the dimeric derivatives may contribute to increased intermolecular interactions and hence result in more stable gelator systems. Also, the differences in the hydrophobicity of the linkers between the sugar headgroups may also affect the gelation properties. Herein, the gelation
properties of the glycolipids are examined and their applications in environmental remediation are explored.

4.2 RESULTS AND DISCUSSION

Two series of dimers were synthesized, the synthetic scheme for the first series is shown in scheme 10. The starting compound 1 was prepared from N-acetyl-D-glucosamine and then utilized to generate headgroup 2 which was reported earlier in the literature.\textsuperscript{226} Compound 2 was reacted with aliphatic and aromatic di-carboxylic acids and phenols via S\textsubscript{N}2 reactions to give the dimers in scheme 10 and scheme 11.

\textbf{Scheme 10.} Synthesis of carbohydrate-based dimeric glycolipids with an ester linkage.
4.2.1 GELATION PROPERTIES OF BOTH SERIES

The gelation properties are summarized in table 8; compounds 3 and 4 were very good gelators for aqueous solutions of DMSO and water in a 1:1 and 1:2 ratios. The isophthalic derivative 5 on the other hand was not a good gelator. It was soluble in aqueous mixtures of water with DMSO and ethanol; the only organic solvents that they were soluble in included ethylene glycol, triethylene glycol and glycerol. The other aromatic ester derivative 6 was less effective at forming a gel when compared to the aliphatic compounds. However, the ether derivatives performed well in DMSO:water mixtures and were also able to form gels in ethylene glycol and glycerol. Overall, the monomeric esters reported previously performed better than the dimeric clusters highlighted herein.\textsuperscript{226} This shows that the dimers do not necessarily allow for increased molecular interactions for better gelation.
Table 8. Gelation test results of compounds 3-8.

<table>
<thead>
<tr>
<th>Cpd. #</th>
<th>H</th>
<th>i-PrOH</th>
<th>EtOH</th>
<th>Glycerol</th>
<th>TEG</th>
<th>EtOH :H₂O (1:2)</th>
<th>EtOH :H₂O (1:1)</th>
<th>DMSO: H₂O (1:2)</th>
<th>DMSO: H₂O (1:1)</th>
<th>H₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>I</td>
<td>PG</td>
<td>PG</td>
<td>G20.0</td>
<td>PG</td>
<td>G20.0</td>
<td>G10.0, T</td>
<td>G5.0, T</td>
<td>G6.7, T</td>
<td>P</td>
</tr>
<tr>
<td>4</td>
<td>P</td>
<td>G5.0, T</td>
<td>G10.0, T</td>
<td>G6.7, c</td>
<td>G20.0, c</td>
<td>G20.0, c</td>
<td>G4.0, T</td>
<td>G4.0, T</td>
<td>G5.0, O</td>
<td>I</td>
</tr>
<tr>
<td>5</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td>6</td>
<td>P</td>
<td>PG</td>
<td>PG</td>
<td>G20.0, T</td>
<td>G20.0, T</td>
<td>S</td>
<td>PG</td>
<td>G10.0, O</td>
<td>G20.0, O</td>
<td>G5.0, O</td>
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<td>I</td>
<td>P</td>
<td>P</td>
<td>G10.0, T</td>
<td>G20.0, c</td>
<td>S</td>
<td>PG</td>
<td>PG</td>
<td>G2.2, T</td>
<td>G4.0, I</td>
</tr>
<tr>
<td>8</td>
<td>I</td>
<td>PG</td>
<td>PG</td>
<td>G10.0, T</td>
<td>G10.0, T</td>
<td>S</td>
<td>G6.7, T</td>
<td>I</td>
<td>G3.3, T</td>
<td>G6.7, T</td>
</tr>
</tbody>
</table>

All compounds were tested starting from 20 mg/mL. G, stable gel at room temperature, the numbers are MGC (MGCs) in mg/mL; P, precipitation; S, soluble; I, insoluble; PG, partial gel; T, translucent; C, clear; O, opaque. Hex-hexane, EG- ethylene glycol, TEG- triethylene glycol. All compounds were insoluble in toluene.

Another series of dimeric glycolipids were synthesized as depicted in scheme 12 from headgroup 9 which was made by reacting compound 1 with bromohexanoyl chloride in the presence of a base. Again, the dimeric molecules were produced via Sₙ2 reactions with both aliphatic and aromatic di-carboxylic acids. There was a longer carbon chain on the sugar as opposed to the first series which had a shorter carbon chain attached to the sugar headgroup. The gel tests on the long chain compounds 10-13 are condensed in table 9. Overall, they performed better in organic solvents such as glycerol and ethylene glycol with lower gelation concentrations when compared to the short chain dimers 3-8.
Scheme 12. Synthesis of carbohydrate-based dimeric gelators from a long chain glycolipid.

Table 9. Gelation test results of compounds 10-13.

<table>
<thead>
<tr>
<th>Cpd. #</th>
<th>Tol</th>
<th>i-PrOH</th>
<th>EtOH</th>
<th>EG</th>
<th>Glyceral</th>
<th>TEG</th>
<th>EtOH :H₂O (1:2)</th>
<th>EtOH :H₂O (1:1)</th>
<th>DMSO: H₂O (1:2)</th>
<th>DMSO: H₂O (1:1)</th>
<th>H₂O</th>
</tr>
</thead>
</table>

All compounds were tested starting from 20 mg/mL. G, stable gel at room temperature, the numbers are MGC (MGCs) in mg/mL; P, precipitation; S, soluble; I, insoluble; PG, partial gel; T, translucent; C, clear; O, opaque. Tol-toluene, EG- ethylene glycol, TEG- triethylene glycol. All compounds were insoluble in hexane.
It was rather interesting to see that increasing the hydrophobic interactions in the long chain dimers also increased their chances of dissolving in water as most of the compounds formed a precipitate after being dissolved in water at high temperatures. The aromatic derivatives 12 and 13 were the best gelators as they were able to gel DMSO:H₂O as well as ethanol:H₂O solutions. A few photographs illustrating the appearance of the gels from both series are shown in figure 79, most were translucent or opaque. The optical microscope images of a few respective gelators were taken under brightfield and are shown in figure 80. A few intertwined fibers were seen but they were not very visible under the optical microscope and this could possibly be due to the fact that they are really small and would need a higher magnification to visualize the morphology of the gel.

![Gel photos of compounds 3, 6, 7, 8 and 11.](image_url)

**Figure 79.** Gel photos of compounds 3, 6, 7, 8 and 11. (a) an opaque gel of compound 3 in DMSO:H₂O (v/v 1:2) 5.0 mg/mL; (b) an opaque gel of compound 6 in DMSO:H₂O (v/v 1:1) 5.0 mg/mL; (c) a translucent gel of compound 7 in DMSO:H₂O (v/v 1:2) 2.5 mg/mL; (d) a translucent gel of compound 8 in DMSO:H₂O (v/v 1:2) 3.3 mg/mL; (e) an opaque gel of compound 11 in ethylene glycol 6.7 mg/mL.
Figure 80. Optical microscope images of various gels taken under brightfield. (a) Compound 3 in DMSO:H₂O (v/v, 1:2), G5.0; (b) Compound 6 in DMSO:H₂O (v/v, 1:1), G5.0; (c) Compound 7 in DMSO:H₂O (v/v, 1:2), G2.5. Images were taken at x50 magnification and the scale bar represents 20µm. (d) Compound 12 in in DMSO:H₂O (v/v, 1:2), G2.5. (x 20 magnification, Scale bar is 50µm).

4.2.2 DYE ABSORPTION STUDIES

In an effort to ascertain the usage of these dimeric gelators in the removal of toxic dyes, two representative gelators from each series were chosen for this study. The gels were somewhat intolerable to water, so they were made in a DMSO:H₂O (v/v, 1:2) solution. For each experiment,
the gels were made and allowed to sit for 30 minutes to 1 h before 2 mL of the aqueous rhodamine B base solution 0.0082 mM was placed on top of the gel and the ability of the gel to remove the dye was monitored over time via UV-Vis spectroscopy. The time dependent absorption spectra and release profile for the experiment with gelator 4 are depicted in figures 81-83.

**Figure 81.** Time dependent UV-Vis spectra of the rhodamine B base solution above the gel of compound 4 and the gel photos throughout the experiment.
The rhodamine B base standard in figure 81 relates to the initially added 2.0 mL of a 0.0082 mM solution of the rhodamine B base dye which gives the maximum absorption. The gel was made by dissolving 10 mg of compound 4 in 2 mL of DMSO:H₂O (v/v, 1:2). The gel was allowed to sit for 1 h before starting the experiment. As shown in figure 81, the gel was able to slowly absorb the dye over time. After approximately 282 h, maximum absorption of the dye was achieved by the gel.

**Figure 82.** The absorbance profile of rhodamine B base by the gel formed by compound 4 for the peak at 554 nm in figure 81. The ratios shown are calculated by using 100% - (the absorbance of the aqueous phase/maximum absorbance).
Figure 83. The absorbance profile of the rhodamine B base that was left in the aqueous solution on top of the gel of compound 4 for the peak at 554 nm in figure 81. The ratios are calculated using the absorbance of the aqueous phase/absorbance of the standard.

Another test was carried out with the gel of compound 12; the gel was made by dissolving 10 mg of the compound in 2 mL of DMSO:water (1:2). The gel was allowed to sit for 30 minutes before starting the experiment. Similar to the first, the rhodamine B base standard relates to the initially added 2.0 mL of a 0.0082 mM solution of the rhodamine B base dye which gives the maximum absorption. Figure 84 illustrates that the gel formed by compound 12 was able to absorb the dye faster than that of compound 4. This may be due to stronger interactions between gelator 12 and the rhodamine B base due to increased π-π interactions since the linker had an additional aromatic ring present which is lacking in compound 4.
Figure 84. Time dependent UV-Vis spectra of the rhodamine B base solution above the gel of compound 12 and the gel photos throughout the experiment.

The results in figures 81-86 demonstrated that these gels can absorb toxic dyes from aqueous solutions. The gel of compound 4 had an absorption efficiency of approximately 70% after 282 h and that of compound 12 reached at 68% at 192 h. They were relatively equal in terms of their absorption efficiencies which confers that the difference in the R groups and the chain length of
the linkers do not significantly affect the capacity of the gels to absorb the dye. The possible interactions governing the gel’s interaction with the dye are π−π interactions and hydrophobic forces that are forming between the aryl rings of the dye and the molecular gelator.

![Absorbance profile of rhodamine B base by the gel formed by compound 12](image)

**Figure 85.** The absorbance profile of rhodamine B base by the gel formed by compound 12 at different time courses for the peak at 554 nm in figure 84. The ratios shown are calculated by using 100% - (the absorbance of aqueous phase/maximum absorbance).
Figure 86. The absorbance profile of the rhodamine B base that was left in the aqueous solution on top of the gel of compound 12 at different time courses for the peak at 554 nm in figure 84. The ratios are calculated using the absorbance of aqueous phase/ absorbance of the standard.

4.2.2 BASE TRIGGERED STUDIES

The efficient gelators with ester linkages could be stimuli responsive through hydrolysis of the ester bond under basic conditions. In order to investigate this phenomenon, a few representative gels were tested. Scheme 13 illustrates the cleavage of the respective short and long chain ester dimers under basic conditions to give the hydrolyzed product 14, whose gel test results were previously reported.226 The gels of compounds 3 and 6 were made in DMSO:H2O (v/v, 1:1) at a concentration of 4.0 mg/mL after which they were allowed to sit for 2 h before adding the different pH solutions. At a pH of 13, the gel of compound 3 hydrolyzed after approximately 4h, that of compound 6 turned to a liquid in about 6 h and the gel of compound 12 broke down in around 144 h with a tiny amount of the gelator still present based on the NMR spectra. This confirms that the
longer chain ester dimers are somewhat more resistant to base hydrolysis based on the time in which hydrolysis was recorded for each. At milder basic conditions of pH 12, full hydrolysis was seen for the gel of compound 3 after 120 h but only partial hydrolysis was seen for compound 6 after 13 days and 5 h with a tiny trace of the gelator still present. The gelators 3 and 12 were also tested for their ability to be cleaved under acidic conditions since they all have an acetal present. Surprisingly, even after roughly 18 days both gels were still quite stable. These results revealed that the gels can be chemically converted to solutions in the presence of bases and could be further studied for their applications as stimuli responsive dimeric clusters.

Scheme 13. Cleavage of the dimeric esters in the presence of a base.
All the compounds were characterized using $^1$H NMR, $^{13}$C NMR, LCMS, FT-IR and melting point. The $^1$H NMR, $^{13}$C NMR and FT-IR spectra of some selected compounds are shown in figures 87-92.

**Figure 87.** $^1$H and $^{13}$C NMR spectra of compound 3.
Figure 88. $^1$H and $^{13}$C NMR spectra of compound 7.
Figure 89. $^1$H and $^{13}$C NMR spectra of compound 12.
**Figure 90.** FT-IR spectrum of compound 3.

**Figure 91.** FT-IR spectrum of compound 7.
Figure 92. FT-IR spectrum of compound 12.

4.3 CONCLUSIONS

The clusters reported herein, are a new class of gelators that could possibly improve gelation properties and hold new applications in different fields. Two series of ester derived dimers and two ether dimers were synthesized and characterized. They were efficient gelators for mixtures of polar organic solvents with water. The first series contained a short aliphatic chain as the linker between the sugars and the second series had a longer carbon chain linker. Overall, the aliphatic derivatives from the short chain dimers performed better than those of the long chain dimers. On the other hand, the aromatic derivatives from the long chain dimers were better gelators when compared to the clusters with the shorter linker. A few representative gelators were also able to absorb cationic dyes from an aqueous solution, confirming their ability to be possibly utilized in environmental remediation. In addition to that, the gels were stable under acidic conditions but
could be cleaved under basic conditions giving rise to stimuli responsive materials. These stimuli responsive gels could be useful for systems where control is a significant factor for different applications. Whilst the dimeric glycolipids did not give better gelators when compared to their monomeric counterparts, the studies are insightful for the structure to gelation properties which are useful for designing intricate sugar-based gelators.

4.4 EXPERIMENTAL SECTION

**General method and materials:** Reagents and solvents were used as they were received from the suppliers. All purification was conducted by flash column chromatography using 230-400 mesh silica gel obtained from Natland International Corporation, unless otherwise noted. The deacetylation reaction was performed in a Mars 6 microwave reactor from CEM Corporation. NMR analysis was conducted using a 400 MHz Bruker NMR spectrometer. Melting point measurements were carried out using a Fisher-Johns Melting Point apparatus. UV-Vis experiments were done using a SHIMADZU UV-1800 Spectrophotometer.

**Optical Microscopy:** A thin slice of the gel was transferred onto a clean glass slide and then left to air dry for a day or so. The gel was then observed under an Olympus BX60M optical microscope at brightfield using an Olympus DP73-1-51 high-performance 17 MP digital camera with pixel shifting and Peltier cooling. The program used to acquire and store the images is CellSens Dimension 1.11.

**Gelation test:** Approximately 2 mg of the desired compound is placed in a one-dram vial and 0.1 mL of the gelation solvent or solution was placed inside the vial to attain a concentration of 20
mg/mL. The vial is then heated until the gelator dissolves fully, sometimes the mixture is sonicated if necessary, to help with dilution. After dissolving, it is left to cool approximately 15 minutes or longer for the gel to form. After this period, if the sample is clear, this is recorded as soluble; if solid reappears, this is recorded as a precipitate; if the sample forms a gel, then the vial is inverted and if there is no solvent flowing this indicates a stable gel; otherwise, it is recorded as an unstable gel. If gelation occurs, another 0.1 mL is added, and the method is repeated until an unstable gel is formed. The MGC, which is the concentration prior to unstable gelation, is obtained.

**Rhodamine B Base dye absorption studies:**

A 0.004 mM solution of rhodamine B base solution was made by diluting a stock solution (0.0082 mM) by adding 4 mL of the stock solution to 18 mL of DI water to make a total volume of 20 mL. The stock solution was made by dissolving 0.0018g of the rhodamine B base compound and dissolving in 100 mL of DI water. From the diluted solution, 2 mL was placed on top of the gel for the study. The gels were prepared using 10 mg of compound 4 and 10 mg of compound 12 in 2.0 mL of DMSO:H₂O (v/v 1:2), they were allowed to sit 30 minutes to an hour before the start of the experiment. The absorbance was taken at different time intervals for the aqueous dye solutions on top of the gels.

**Base Triggered Studies:**

4 mg of compound 3 or 6, or 12 was weighed out in a one-dram vial and 0.5 mL of DMSO:H₂O (v/v, 1:1) was added to make the gel (two gels were made). After 2 h, 0.5 mL of pH 12 and 13 solutions were added to the vials and the gels were observed every hour to record any
decomposition that occurred. After the gels were broken down the resulting compound was extracted with 2 mL of DCM and a proton NMR spectrum was taken.

**Acid Stability Studies:**

4 mg of compound 3 was weighed out in a one-dram vial and 0.5 mL of DMSO:H₂O (1:1) was added to make the gel (two gels were made). After 2 h, 0.5 mL of pH 2 and 4 solutions were added to the vials and the gels were observed every hour to record any decomposition that occurred. The same protocol was used for compound 12 (4 mg)

**General Procedure for the amide derivative 3-6 synthesis from headgroup 2**

Compound 2 was synthesized by a previously reported literature procedure.²²⁶ In a 50 mL round bottom flask equipped with a drying tube; the carboxylic acid (2 equiv) was added to the flask, followed by DIEA (2.0 equiv) and 1-2 mL of anhydrous acetonitrile/DMF. The reaction mixture was stirred at rt for 30 minutes and then the headgroup, compound 2 (about 100 mg, 0.24 mmol, 1 equiv) was added with 1-2 mL of anhydrous acetonitrile/DMF. The reaction mixture was then stirred for about 6-24 h at 70-75 °C. At which time TLC and ¹H NMR spectroscopy were used to monitor the progress of the reaction. If not complete, the reaction mixture was stirred for longer time. After the starting material was fully converted to the product, the reaction mixture was cooled and concentrated on a rotavap to remove the solvent. The crude product was worked up with DCM and 5% or saturated NaHCO₃ solution then with water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed to obtain the crude product. The crude product was purified by flash column chromatography on silica gel using a gradient of
dichloromethane and methanol. The quantities of reagents and characterization data are given below, detailed procedures are not given unless different conditions are used.

**Synthesis of dimer derivative 3**

Adipic acid (0.0134 g, 0.092 mmol, 1 equiv.) followed by DIEA (0.069 mL, 0.41 mmol, 2 equiv.) and 2 mL of anhydrous acetonitrile were added in a 50 mL round bottom flask and the reaction mixture was allowed to stir at rt for 25 minutes. After this, compound 2 (0.0815 g, 0.20 mmol, 2.2 equiv.) was added along with 2.5 mL of anhydrous acetonitrile. The reaction mixture was left to stir for 25 h at 75 °C during which 2 mL of anhydrous acetonitrile was added. After the starting material was fully consumed, acetonitrile was removed from the reaction mixture via the rotavap. Workup was done using DCM (15 mL x 3)/ sat. NaHCO₃ (10 mL) and then with water. The combined organic layer was dried over Na₂SO₄ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 3.5% MeOH/DCM to afford a white solid (67.1 mg, 93%) as the desired product. (Rᵣ = 0.37 in 5% MeOH/DCM). mp 209-211 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.54-7.46 (m, 4H), 7.42-7.32 (m, 6H), 6.37 (d, J = 8.5 Hz, 2H), 5.52 (s, 2H), 4.74 (d, J = 3.8 Hz, 2H), 4.66-4.51 (m, 4H), 4.32-4.16 (m, 4H), 3.90 (t, J = 9.5 Hz, 2H), 3.83-3.69 (m, 4H), 3.50 (t, J = 8.9 Hz, 2H), 3.40 (s, 6H), 2.56-2.38 (m, 4H), 1.84-1.70 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 172.0, 167.8, 137.1, 129.3, 128.3, 126.3, 101.9, 98.7, 81.9, 69.9, 68.8, 63.0, 62.5, 55.4, 53.6, 33.4, 24.0 LC-MS m/z calcd. for C₃₈H₄₉N₂O₁₆ [M + H] 789.30, found 789.
Synthesis of dimer derivative 4

Sebacic acid (0.0174 g, 0.086 mmol, 1 equiv.) followed by DIEA (0.065 mL, 0.38 mmol, 2 equiv.) and 2 mL of anhydrous acetonitrile were added in a 50 mL round bottom flask and the reaction mixture was allowed to stir at rt for 25 minutes. After this, compound 2 (0.0762 g, 0.19 mmol, 2.2 equiv.) was added along with 2.5 mL of anhydrous acetonitrile. The reaction mixture was left to stir for 23 h at 75 °C, after 24 h, the temperature was increased to 85 °C and the reaction was stopped at 30 h. After the starting material was fully consumed, acetonitrile was removed from the reaction mixture via the rotavap. Workup was done using DCM (20 mL x 3)/ sat. NaHCO₃ (10 mL) and then with water. The combined organic layer was dried over Na₂SO₄ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 3% MeOH/DCM to afford a white solid (65.6 mg, 90%) as the desired product. (Rf = 0.37 in 5% MeOH/DCM). mp 181-183 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.53-7.45 (m, 4H), 7.42-7.31 (m, 6H), 6.40 (d, J = 8.9 Hz, 2H), 5.56 (s, 2H), 4.73 (d, J = 3.8 Hz, 2H), 4.66-4.53 (m, 4H), 4.34-4.20 (m, 4H), 3.92 (t, J = 9.6 Hz, 2H), 3.84-3.74 (m, 4H), 3.59 (t, J = 9.1 Hz, 2H), 3.41 (s, 6H), 2.42 (t, J = 7.4 Hz, 4H), 1.70-1.62 (m, 4H), 1.38-1.31 (m, 8H); ¹³C NMR (100 MHz, CDCl₃) δ 172.2, 168.1, 137.1, 129.2, 128.3, 126.3, 102.0, 98.7, 81.9, 70.2, 68.8, 62.8, 62.5, 55.4, 53.6, 33.9, 28.8, 28.8, 24.7. LC-MS m/z calcd. for C₄₂H₅₇N₂O₁₆ [M + H] 845.36, found 845.3.

Synthesis of dimer derivative 5

Isophthalic acid (0.0151 g, 0.085 mmol, 1 equiv.) followed by DIEA (0.032 mL, 0.19 mmol, 2.2 equiv.) and 2 mL of anhydrous acetonitrile were added in a 50 mL round bottom flask and the reaction mixture was allowed to stir at rt for 30 minutes. After this, compound 2 (0.0749 g, 0.19 mmol, 2.2 equiv.) was added along with 2 mL of anhydrous acetonitrile. The reaction mixture was
allowed to stir for up to 27 h at 75 °C during which at 5.5 h, 1 mL of anhydrous acetonitrile was added and at 8 h, 2 mL was added. After the starting material was fully consumed, acetonitrile was removed from the reaction mixture via the rotavap. The compound was sonicated in MeOH and then filtered to afford a white solid as the desired product in quantitative yield. mp >265 °C. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.57 (bs, 1H), 8.32-8.27 (m, 2H), 7.75 (t, \(J = 7.8\), 1H), 7.50-7.42 (m, 4H), 7.42-7.33 (m, 6H), 5.62 (s, 2H), 4.84 (bs, 4H), 4.67 (d, \(J = 3.5\)Hz, 2H), 4.22-4.14 (m, 2H), 3.92-3.84 (m, 2H), 3.79-3.68 (m, 4H), 3.67-3.59 (m, 2H) 3.52 (t, \(J = 9.2\) Hz, 2H), expected peak under water from the deuterated solvent 3.37 (s, 6H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 166.6, 164.5, 137.7, 134.0, 130.0, 128.9, 128.0, 126.4, 100.9, 98.6, 81.8, 79.1, 68.0, 67.4, 62.9, 62.5, 54.9, 54.2. LC-MS m/z calcd. for C\(_{20}\)H\(_{22}\)NO\(_8\) [M]\(^{2+}\) 404.64, found 404.8 [M]\(^{2+}\).

**Synthesis of dimer derivative 6**

Potassium biphthalate (0.0143 g, 0.07 mmol, 1 equiv.) followed by DIEA (0.013 mL, 0.077 mmol, 1.2 equiv.) and 2 mL of anhydrous acetonitrile were added in a 50 mL round bottom flask and the reaction mixture was allowed to stir at rt for 25 minutes. After this, compound 2 (0.0567 g, 0.14 mmol, 2.2 equiv.) was added along with 1 mL of anhydrous acetonitrile. The reaction mixture was left to stir for 47.5 h at 74-80 °C. After the starting material was fully consumed, acetonitrile was removed from the reaction mixture via the rotavap. Workup was done using DCM (15 mL x 3)/ sat. NaHCO\(_3\) (5 mL) and then with water. The combined organic layer was dried over Na\(_2\)SO\(_4\) (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 3.5% MeOH/DCM to afford a white solid (32.3 mg, 57%) as the desired product. \(R_t = 0.28\) in 3% MeOH/DCM). mp 214-216 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.90-7.80 (m, 2H), 7.69-7.62 (m, 2H), 7.52-7.44 (m, 4H), 7.38-7.31 (m, 6H), 6.66
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(d, J = 8.8 Hz, 2H), 5.46 (s, 2H), 4.86 (bs, 4H), 4.76 (d, J = 3.6 Hz, 2H), 4.29-4.17 (m, 4H), 3.94 (t, J = 9.7 Hz, 2H), 3.81-3.66 (m, 4H), 3.44 (t, J = 9.1 Hz, 2H), 3.33 (s, 6H); 13C NMR (100 MHz, CDCl3) δ 167.4, 166.7, 137.3, 132.0, 130.9, 129.5, 129.2, 128.3, 126.4, 101.8, 98.8, 81.7, 69.3, 68.8, 64.2, 62.5, 55.4, 54.0, 29.7. LC-MS m/z calcd. for C40H45N2O16 [M + H] 809.27, found 809.

Synthesis of dimer derivative 7

Compound 2 (0.0759 g, 0.19 mmol, 2.2 equiv.) was added to a small 50 mL round bottom flask and dissolved in DMF. Potassium bicarbonate (0.0237 g, 0.17 mmol, 2 equiv.) and catechol (0.0095 g, 0.09 mmol, 1 equiv.) were then added to the flask and the reaction mixture was allowed to stir 32 h at rt after which it was heated to 54 °C until approx. 59 h. After the starting material was fully consumed, acetonitrile was removed from the reaction mixture via the rotavap. Workup was done using DCM (10 mL x 3)/5% NaHCO3 solution (5 mL) and then with water. The combined organic layer was dried over Na2SO4 (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 4% MeOH/DCM to afford a white solid (49.3 mg, 73%) as the desired product. (Rf = 0.43 in 5% MeOH/DCM). mp >265 °C turns brown. 1H NMR (400 MHz, CDCl3 with a drop of D-MeOH) δ 7.49-7.44 (m, 4H), 7.36-7.31 (m, 6H), 7.12 (d, J = 8.8 Hz, 2H), 7.05-6.93 (m, 4H), 5.50 (s, 2H), 4.75 (d, J = 3.7 Hz, 2H), 4.65 (d, J = 15.3 Hz, 2H), 4.61 (d, J = 15.3 Hz, 2H), 4.29-4.20 (m, 4H), 4.04 (t, J = 9.7 Hz, 2H), 3.84-3.69 (m, 4H), 3.55 (t, J = 9.2 Hz, 2H) 3.30 (s, 6H); 13C NMR (100 MHz, CDCl3) δ 169.2, 147.8, 137.1, 129.2, 128.2, 126.3, 123.3, 115.9, 102.0, 98.8, 81.9, 69.3, 69.1, 68.8, 62.6, 55.4, 53.8. LC-MS m/z calcd. for C38H45N2O14 [M + H] 753.28, found 753.
**Synthesis of dimer derivative 8**

Compound 2 (0.0917 g, 2.5 equiv, 0.23 mmol) was added to a small 50 mL round bottom flask followed by potassium carbonate (0.0634 g, 5 equiv, 0.46 mmol) along with 4 mL of anhydrous DMF. Afterwards, hydroquinone (0.0104 g, 1 equiv, 0.09 mmol) was added and the mixture was allowed to stir at rt for 12 h. After the starting material was fully consumed, the DMF was removed from the reaction mixture by drying under air. Workup was done using DCM and cold water. The combined organic layer was dried over Na$_2$SO$_4$ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 2.5% MeOH/DCM to afford a white solid (56.9 mg, 80%) as the desired product. (R$_f$ = 0.31 in 3% MeOH/DCM). mp >270 °C. $^1$H NMR (400 MHz, CDCl$_3$ with a drop of D-MeOH) δ 7.53-7.44 (m, 4H), 7.43-7.33 (m, 6H), 6.91 (s, 4H), 6.85 (d, J = 9.2 Hz, 2H), 5.54 (s, 2H), 4.71 (d, J = 3.8 Hz, 2H), 4.53 (d, J = 15.1 Hz, 2H), 4.49 (d, J = 15.1 Hz, 2H), 4.36-4.24 (m, 4H), 3.93 (t, J = 9.6 Hz, 2H), 3.84-3.73 (m, 4H), 3.58 (t, J = 9.1 Hz, 2H), 3.37 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.3, 152.4, 137.0, 129.3, 128.3, 126.3, 116.1, 102.0, 98.8, 82.0, 69.9, 68.8, 68.1, 62.5, 55.4, 53.4, 53.3. LC-MS m/z calcd. for C$_{38}$H$_{45}$N$_2$O$_4$ [M + H] 753.28, found 753.

**Synthesis of the 4,6-Benzyl protected headgroup 9**

Compound 1 (0.2649 g, 1 equiv, 0.94 mmol) was added to a 100 mL round bottom flask along with 8 mL of DCM (anhydrous), DIPEA (0.25 mL, 1.5 equiv) and potassium carbonate (0.3905 g, 3 equiv, 2.83 mmol). This mixture was stirred at 0°C for approximately 30 minutes, during this time 6-bromohexanoyl chloride (1.2 equiv) was diluted with DCM (anhydrous). Afterwards, it was added in a dropwise manner to the round bottom flask at 0 °C. The reaction mixture was then stirred for an additional 2.5 h from 0 to rt. After the starting material was fully consumed, the DCM
was removed from the reaction mixture via the rotavap. Workup was done using DCM (15 mL x 3)/5% sodium bicarbonate and then with water (10 mL). The combined organic layer was dried over Na₂SO₄ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 2.5% MeOH/DCM to afford a white solid 400.7 mg, 93%) as the desired product. (Rᵣ = 0.43 in 3% MeOH/DCM). mp 190-192 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.55–7.45 (m, 2H), 7.43–7.30 (m, 3H), 5.85 (d, J = 8.6 Hz, 1H), 5.57 (s, 1H), 4.73 (d, J = 3.8 Hz, 1H), 4.33–4.19 (m, 2H), 3.91 (t, J = 9.6 Hz, 1H), 3.84–3.73 (m, 2H), 3.59 (t, J = 9.0 Hz, 1H), 3.46–3.37 (m, 5H), 2.28 (t, J = 7.4 Hz, 2H), 1.93–1.83 (m, 2H), 1.75–1.65 (m, 2H), 1.54–1.45 (m, 2H); ¹³C (100MHz, CDCL₃) δ 174.1, 137.1, 129.2, 128.3, 126.3, 102.0, 98.8, 82.1, 70.8, 68.8, 62.4, 55.3, 54.0, 36.3, 33.6, 32.4, 27.6, 24.6. LC-MS m/z calcd. for C₂₀H₂₉BrNO₆ [M + H] 458.11, found 458.

**General Procedure for the ester derivatives 10-13 synthesis from headgroup 9**

In a 50 mL round bottom flask equipped with a drying tube; the carboxylic acid (2 equiv) was added to the flask, followed by DIEA/potassium carbonate (2.0 equiv) and 1-2 mL of anhydrous acetonitrile/DMF. The reaction mixture was stirred for at rt for 30 minutes and then the headgroup, compound 9 (about 100 mg, 0.24 mmol, 1 equiv) was added with 1-2 mL of anhydrous acetonitrile/DMF. The reaction mixture was then stirred for about 6-24 h at 70-75 °C. At which time TLC and ¹H NMR spectroscopy were used to monitor the progress of the reaction. If not complete, the reaction mixture was stirred for a longer time. After the starting material was fully converted to the product, the reaction mixture was cooled and concentrated on a rotavap to remove the solvent. The crude product was worked up with DCM and 5% or saturated NaHCO₃ solution then with water. The organic phase was dried over anhydrous sodium sulfate and the solvent was
removed to obtain the crude product. The crude product was purified by flash column chromatography on silica gel using a gradient of dichloromethane and methanol. The quantities of reagents and characterization data are given below, detailed procedures are not given unless different conditions are used.

**Synthesis of ester derivative 10**

Compound 9 (0.0530 g, 0.12 mmol, 1 equiv.) followed by potassium carbonate (0.0165 g, 0.12 mmol, 2 equiv.) and 2 mL of anhydrous DMF were added in a 50 mL round bottom flask and the reaction mixture was allowed to stir at rt for 30 minutes. After this, Adipic acid (0.0080 g, 0.055 mmol, 1 equiv.) was added and 1.0 mL of anhydrous acetonitrile. The reaction mixture was left to stir for 29 h at 65 °C. After the starting material was fully consumed, acetonitrile was removed from the reaction mixture via the rotavap. Workup was done using DCM (10 mL x 3)/ 5% NaHCO₃ (5 mL) and then with water. The combined organic layer was dried over Na₂SO₄ (anhdyrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 4% MeOH/DCM to afford a white solid (23.9 mg, 49%) as the desired product. (Rᵋ = 0.14 in 3% MeOH/DCM). mp 157-159 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.54-7.45 (m, 4H), 7.41-7.31 (m, 6H), 5.96 (d, J = 8.6 Hz, 2H), 5.55 (s, 2H), 4.73 (d, J = 3.8 Hz, 2H), 4.35-4.15 (m, 4H), 4.06 (t, J = 6.6 Hz, 4H), 3.90 (t, J = 9.6 Hz, 2H), 3.83-3.72 (m, 4H), 3.58 (t, J = 9.0 Hz, 2H), 3.40 (s, 6H), 2.34-2.23 (m, 8H), 1.75-1.59 (m, 12H), 1.44-1.34 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 174.2, 173.4, 137.2, 129.2, 128.3, 126.3, 101.9, 98.9, 82.1, 70.6, 68.9, 64.2, 62.4, 55.3, 54.1, 36.4, 34.0, 28.4, 25.5, 25.1, 24.4. LC-MS m/z calcd. for C₄₆H₆₅N₂O₁₆ [M + H] 901.43, found 901.
Synthesis of ester derivative 11

Sebacic acid (0.0159 g, 0.079 mmol, 1 equiv.) followed by potassium carbonate (0.0224 g, 0.16 mmol, 2 equiv.) and 1.5 mL of anhydrous DMF were added in a 50 mL round bottom flask and the reaction mixture was allowed to stir at rt for 30 minutes. After this, compound 9 (0.0790 g, 0.17 mmol, 2.2 equiv.) was added and 1.5 mL of anhydrous DMF. The reaction mixture was left to stir for 48 h at 70-79 °C. After the starting material was fully consumed, DMF was removed from the reaction mixture via drying under air. Workup was done using DCM (10 mL x 3)/5% NaHCO₃ (5 mL) and then with water. The combined organic layer was dried over Na₂SO₄ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 3% MeOH/DCM to afford a white solid (29.9 mg, 41%) as the desired product. (Rᵣ = 0.20 in 3% MeOH/DCM). mp 132-134 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.52-7.47 (m, 4H), 7.39-7.33 (m, 6H), 5.89 (d, J = 8.6 Hz, 2H), 5.56 (s, 2H), 4.73 (d, J = 3.8 Hz, 2H), 4.32-4.18 (m, 4H), 4.06 (t, J = 6.6 Hz, 4H), 3.90 (t, J = 9.6 Hz, 2H), 3.84-3.73 (m, 4H), 3.58 (t, J = 8.9 Hz, 2H), 3.40 (s, 6H), 2.31-2.24 (m, 8H), 1.71-1.58 (m, 12H), 1.45-1.35 (m, 4H), 1.32-1.17 (m, 8H); ¹³C NMR (100 MHz, CDCl₃) δ 174.2, 173.9, 137.9, 137.2, 129.2, 128.3, 126.3, 101.9, 98.8, 82.1, 70.7, 68.9, 64.0, 62.4, 55.3, 54.1, 36.4, 34.3, 29.0, 28.4, 25.5, 25.1, 24.9.

LC-MS m/z calcd. for C₅₀H₇₃N₂O₁₆ [M + H] 957.49, found 957.

Synthesis of ester derivative 12

Isophthalic acid (0.0085g, 0.051 mmol, 1 equiv.) followed by potassium carbonate (0.0156 g, 0.11 mmol, 2 equiv.) and 2 mL of anhydrous DMF were added in a 50 mL round bottom flask and the reaction mixture was allowed to stir at rt for 30 minutes. After this, the bromide headgroup 9 (0.0514 g, 0.11 mmol, 2.2 equiv.) was added and 1 mL of anhydrous DMF. The reaction mixture
was left to stir for 24 h and 15 minutes at 72-80 °C. The NMR and TLC at 23 h showed that the starting material was consumed. After the starting material was fully consumed, DMF was removed from the reaction mixture via drying under air. Workup was done using DCM (15 mL x 3)/ sat. NaHCO₃ (5 mL) and then with water. The combined organic layer was dried over Na₂SO₄ (anhydrous), filtered and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 3.5% MeOH/DCM to afford a white solid (40.1 mg, 85%) as the desired product. (R₉ = 0.25 in 3% MeOH/DCM). mp 182-184 °C. ¹H NMR (400 MHz, CDCl₃) δ; 8.64 (s, 1H), 8.21 (dd, J = 1.8 Hz, J = 1.5 Hz, 2H), 7.57-7.46 (m, 5H), 7.40-7.30 (m, 6H), 5.97 (d, J = 8.5 Hz, 2H), 5.54 (s, 2H), 4.73 (d, J = 3.7 Hz, 2H), 4.34 (t, J = 6.4 Hz, 4H), 4.30-4.17 (m, 4H), 3.91 (t, J = 9.6 Hz, 2H), 3.82-3.71 (m, 4H), 3.58 (t, J = 8.9 Hz, 2H), 3.38 (s, 6H), 2.30 (t, J = 7.4 Hz, 4H), 1.85-1.72 (m, 8H), 1.56-1.49 (m, 4H);¹³C NMR (100 MHz, CDCl₃) δ 174.1, 165.8, 137.2, 133.8, 130.8, 130.5, 129.2, 128.7, 128.3, 126.4, 101.9, 98.9, 82.0, 70.5, 68.9, 65.1, 62.4, 55.3, 54.1, 36.4, 28.4, 25.7, 25.2. LC-MS m/z calcd. for C₄₈H₆₁N₂O₁₆ [M + H] 921.39, found 921.

**Synthesis of ester derivative 13**

Potassium biphthalate (0.0085 g, 0.042 mmol, 1 equiv.) followed by potassium carbonate (0.0113 g, 0.082 mmol, 2 equiv.) and 1 mL of anhydrous DMSO were added in a 50 mL round bottom flask and the reaction mixture was allowed to stir at rt for 30 minutes. After this, the bromide headgroup 9 (0.0413 g, 0.090 mmol, 1.0 equiv.) was added and 2 mL of anhydrous DMSO. The reaction mixture was left to stir for 27 h at 56-60 °C. The NMR and TLC at 24 h showed that the reaction was complete. Workup was done by adding sat. NaHCO₃ (5 mL) to the reaction and then extracted with DCM. The combined organic layer was dried over Na₂SO₄ (anhydrous), filtered
and concentrated to give the crude, which was purified by column chromatography using eluent from pure DCM to 3% MeOH/DCM to afford a white solid (12.9 mg, 34%) as the desired product. (Rf = 0.20 in 3% MeOH/DCM). mp 152-154 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(7.74 - 7.65\) (m, 2H), \(7.54 - 7.45\) (m, 6H), \(7.38 - 7.31\) (m, 6H), \(6.07\) (d, \(J = 8.5\) Hz, 2H), \(5.52\) (s, 2H), \(4.72\) (d, \(J = 3.7\) Hz, 2H), \(4.33 - 4.16\) (m, 8H), \(3.88\) (t, \(J = 9.6\) Hz, 2H), \(3.80 - 3.71\) (m, 4H), \(3.57\) (t, \(J = 9.0\) Hz, 2H), \(3.36\) (s, 6H), \(2.26\) (t, \(J = 7.4\) Hz, 4H), \(1.79 - 1.64\) (m, 8H), \(1.49 - 1.41\) (m, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 174.2, 167.7, 137.2, 132.2, 131.0, 129.1, 128.9, 128.2, 126.4, 101.9, 98.9, 82.0, 70.3, 68.9, 65.6, 62.5, 55.3, 54.2, 36.4, 29.7, 28.3, 25.5, 25.2. LC-MS m/z calcd. for C\(_{48}\)H\(_{61}\)N\(_2\)O\(_{16}\) [M + H] 921.39, found 921.
CHAPTER 5

CONCLUSIONS AND FUTURE RESEARCH

The utilization of gels as advanced soft materials holds great promise especially in biomedical sciences as the development of novel drug delivery systems is needed. Many drugs interact with other compounds causing side effects or are metabolized before reaching their site of action. Improved, targeted drug delivery can help to reduce these disadvantages. Environmental remediation is also a crucial area that needs to be investigated. Pollution caused by the leaching of dyes into water reserves and oil spills can affect the quality of water available to humans. The development of materials that can absorb dyes, oils and other chemicals will assist with cleaning up water to enhance its potability for people around the world. Another potential application for these materials is to act as a scaffold for enzyme immobilization. Enzyme immobilization is necessary for several reactions in commercialized industries and allows for efficient and cheaper synthetic methods. Current research on materials used to immobilize enzymes focuses mainly on polymers or other materials. Low molecular weight gelators are an untapped resource for enzyme immobilization and should not be overlooked. The objective here was to utilize novel, biologically compatible, carbohydrate-based materials in drug delivery, enzyme immobilization and environmental remediation applications.

My research encompasses the design, synthesis, and study of novel carbohydrate-based compounds as gelators for various applications. I employed a wide range of interdisciplinary approaches to answer my research questions, from synthetic chemistry to enzymatic assays. This
dissertation has presented novel research on the development of carbohydrate-based soft materials and their use in different applications. The research herein adds knowledge and sheds light on the design architecture of effective gelators that other scientists in the field can benefit from.

The first chapter presented a comprehensive overview of the literature pertaining to supramolecular gelators. It highlighted the techniques utilized in the design strategy and characterization of these molecules. The low molecular weight gelators derived from carbohydrates with different molecular architectures were reviewed in great detail including those derived from amino-acids or peptides, salts, cholesterol and other steroids. Gelators that are responsive to stimuli such as enzymes, light, pH and temperature were described. Examples of applications for the gelators in drug delivery, tissue engineering, environmental remediation, enzyme immobilization and as antibacterial agents were also reviewed in chapter one.

The second chapter highlighted effective gelators from a series of hybrid glucosamine derivatives containing amide and ester groups. The objective of the project was to obtain low molecular weight gelators containing ester functionalities that could act as stimuli responsive gels, in the presence of bases or lipases for applications in drug delivery and environmental remediation. A series of gelators with an ester functional group, were generated from N-acetyl-D-glucosamine and they were able to form gels in both in organic solvents, water, as well as aqueous solutions. Both aliphatic and aromatic esters were created to understand the impact of the R group on the gelation properties, and it was found that overall, the aromatic derivatives performed better than the aliphatic esters. One of the short linear alkyl chain derivatives was able to form a hydrogel and performed better than the compounds with a longer alkyl chain. Altogether, the compounds
demonstrated their potential to be utilized as stimuli responsive systems for drug delivery as they were hydrolyzed under basic conditions as shown in figure 93 and could entrap and release drugs. They were also able to interact with cationic dyes and may have possible applications in dye removal for environmental remediation. Since these gelators worked well for drug delivery, it would be interesting to investigate the cytotoxicity effects to confirm their biocompatibility. Also, other dyes could be explored especially anionic dyes to assess if the gels are selective for removing specific types of dyes and expand their utilization in environmental remediation.

**Figure 93.** A diagram highlighting a few results from chapter two.

The second research project discussed in chapter three, built on the first by introducing slight modifications into the gelator structure to evaluate the impact on the gelation properties. The objective was to obtain gelators containing ester, ether and amine functional groups, which could
be utilized for enzyme immobilization and possibly drug delivery. Chapter three reported the synthesis and modification of carbohydrates to form a series of functionalized molecules which were also efficient gelators as well as a few salt-based gelators. The amine derivatives were not as effective as the ethers and esters, but the aniline derivative turned out to be the best performing amine and it was chosen to make a few amine salts. The salts were also gelators in aqueous solutions and a couple had fluorescent properties. The drug release studies confirmed their potential utilization in drug delivery and the results from the enzyme immobilization depicted in figure 94 also showed that the gels can encapsulate enzymes such as amylase with retention of its activity. These gels have great promise for many applications and need to be investigated further. The salts could be studied further for dye removal since they are charged and may have stronger interactions with oppositely charged dyes. Also, other amines and carboxylic acids could be examined for the generation of a larger library of salt-based gelators. In addition to that, the salts could be evaluated further for their ability to conduct electricity and confirm any potential applications in several devices. Consequently, a wider range of enzymes could be investigated for enzyme immobilization which is an important area of research.
The last chapter discloses findings for two series of dimeric glucosamine derivatives containing ester and ether functional groups with both aliphatic and aromatic linkers. The presence of two sugar units in the molecule may contribute to increased intermolecular interactions and hence result in more stable gelator systems; this was proven by their enhanced stability in basic conditions when compared to their monomeric counterparts. Both series gave efficient gelators mostly for aqueous solutions of polar organic solvents and were also responsive to basic conditions as evidenced by the hydrolysis of the esters. The gelators were also able to absorb cationic dyes from aqueous solutions illustrating their potential to be utilized in the removal of toxic dyes from wastewater as shown in figure 95. Overall, the project confirms that dimeric compounds from carbohydrates can also be useful gelators and presents a good design strategy for generating new classes of gelator molecules. These compounds could be further studied for the removal of other types of dyes as well as they could be examined further for possible applications in drug delivery and their biocompatibility.
The gelators presented in my research, demonstrated success in the structure-based design to obtain stimuli-responsive soft materials. The hybrid gelator systems presented throughout this dissertation, formed efficient gels in a wide panel of solvents with most having a fibrous morphology. The overall results validated that the sugar-based gelators have the potential to be utilized in enzyme immobilization, as controlled drug delivery carriers for various applications and as bio sorbents in environmental remediation.

Figure 95. A schematic illustration displaying the dye absorption capabilities of the gels presented in chapter four.
REFERENCES


# APPENDIX

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