Design, Synthesis and Characterization of Carbohydrate Based Macrocycles, Photo Responsive Derivatives, and Glycoconjugates Based Low Molecular Weight Gelators

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DESIGN, SYNTHESIS AND CHARACTERIZATION OF CARBOHYDRATE BASED
MACROCYCLES, PHOTO RESPONSIVE DERIVATIVES, AND
GLYCOCONJUGATES BASED LOW MOLECULAR WEIGHT GELATORS

by

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Approved by:

Guijun Wang (Director)
James Lee (Member)
Erin Purcell (Member)
Bala Ramjee (Member)
Joshua Choi (Member)
ABSTRACT

DESIGN, SYNTHESIS AND CHARACTERIZATION OF CARBOHYDRATE BASED MACROCYCLES, PHOTO RESPONSIVE DERIVATIVES, AND GLYCOCONJUGATES BASED LOW MOLECULAR WEIGHT GELATORS

Surya Bahadur Adhikari
Old Dominion University, 2021
Director: Dr. Guijun Wang

Functional glycoconjugates are important classes of compounds with many applications in different research fields. Our lab has been studying the synthesis and applications of different classes of glycoconjugates ranging from macrocycles to sugar heterocycle derivatives. Due to the importance of these compounds, our research is based on development of synthetic methods for various carbohydrate derivatives. This dissertation includes introduction and overview of projects, followed by the synthesis and studies of several different series of glycomacroclactones. The second project focuses on two classes of photoresponsive molecules, the coumarins and diarylethenes. The third project involves the synthesis and self-assembling properties of isoxazole-based glycoconjugates.

Macrocycles are important compounds for drug discovery and development. They are also useful in supramolecular chemistry and materials science. Using the copper catalyzed azide alkyne cycloaddition reactions (CuAACs), “click chemistry”, several glycomacrocycles have been synthesized previously. Here the synthesis and characterization of two new series of glycomacrolactones are reported. The methods for effective macrolactonization steps were established and the synthesized macrolactones were analyzed for applications in molecular recognition and catalysis.
In the third chapter, to expand the research into obtaining functional new materials, two classes of photo-responsive compounds are studied. The first class focuses on coumarin derivatives, which showed fluorescent properties and can be used as fluorescent probes for biomedical research. Using a sugar gelator template, several sugar-coumarin derivatives were shown to be effective low molecular weight gelators (LMWGs). The second class involves the diarylethene based photochromic molecules, which can be used as molecular switches for a variety of applications including optical memory devices. The preparation of diarylethene derivatives is discussed, their applications in hybrid optical materials are being studied through collaboration.

Besides the coumarin-sugar conjugates and glycosyl triazole derivatives, using the demonstrated carbohydrate building blocks, we have also synthesized and characterized a new series of glycosyl isoxazole derivatives. The current study focuses on the synthetic method and the preliminary gelation properties of these sugar heterocycle derivatives. These compounds are expected to have utilities in various research fields, which will be further explored in the future.
This dissertation is dedicated to my family and friends for all their love and support.

Father: \textit{Tanka B. Adhikari}

Mother: \textit{Jamuna D. Adhikari}

Wife: \textit{Binu Shrestha}
ACKNOWLEDGEMENTS

I would like to extend my deepest gratitude to my advisor, Dr. Guijun Wang for her support and guidance throughout my time as graduate student. I feel lucky to be part of her lab for the past six years. She has provided me with encouragement and patience throughout my time at ODU.

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I’d like to recognize the help that I received from our staff members Tammy, Janice, Alicia, Kristi, Michelle, and Dana.

Special thanks to my family for their unparalleled support.

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<table>
<thead>
<tr>
<th><strong>NOMENCLATURE</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BODIPY</strong></td>
<td>Boron-dipyrrromethene (4,4-difluoro-4-bora-3a,4a-diaza-s-indacene)</td>
</tr>
<tr>
<td><strong>DCM</strong></td>
<td>Dichloromethane</td>
</tr>
<tr>
<td><strong>DMAP</strong></td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td><strong>DMF</strong></td>
<td>N, N-dimethylformamide</td>
</tr>
<tr>
<td><strong>DMSO</strong></td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td><strong>CDCl₃</strong></td>
<td>Deuterated chloroform</td>
</tr>
<tr>
<td><strong>EtOH</strong></td>
<td>Ethanol</td>
</tr>
<tr>
<td><strong>Et₃N</strong></td>
<td>Triethylamine</td>
</tr>
<tr>
<td><strong>H₂O</strong></td>
<td>Water</td>
</tr>
<tr>
<td><strong>HRMS</strong></td>
<td>High resolution mass spectrometry</td>
</tr>
<tr>
<td><strong>IPA</strong></td>
<td>Isopropanol</td>
</tr>
<tr>
<td><strong>LCMS</strong></td>
<td>Liquid chromatography mass spectrometry</td>
</tr>
<tr>
<td><strong>MP</strong></td>
<td>Melting point</td>
</tr>
<tr>
<td><strong>NaAsc</strong></td>
<td>Sodium ascorbate</td>
</tr>
<tr>
<td><strong>NI</strong></td>
<td>Naphthalimide</td>
</tr>
<tr>
<td><strong>NMR</strong></td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td><strong>PDI</strong></td>
<td>Perylenediimide</td>
</tr>
<tr>
<td><strong>PTSA</strong></td>
<td>p-Toluenesulfonic acid</td>
</tr>
<tr>
<td><strong>rt</strong></td>
<td>Room temperature</td>
</tr>
<tr>
<td><strong>SEM</strong></td>
<td>Scanning electron microscope</td>
</tr>
<tr>
<td><strong>t-BuOH</strong></td>
<td>Tertiary butyl alcohol</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TPE</td>
<td>Terephenylethylene</td>
</tr>
<tr>
<td>UV-Vis</td>
<td>Ultraviolet and visible</td>
</tr>
</tbody>
</table>
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. BACKGROUND AND LITERATURE REVIEW</strong></td>
<td>1</td>
</tr>
<tr>
<td>1.1 INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1.2 INTRODUCTION OF MACROCYCLES</td>
<td>2</td>
</tr>
<tr>
<td>1.2.1 METHODS OF MACROCYCLE SYNTHESIS</td>
<td>4</td>
</tr>
<tr>
<td>1.2.2 CARBOHYDRATE-BASED MACROCYCLES</td>
<td>8</td>
</tr>
<tr>
<td>1.3 MOLECULAR SELF-ASSEMBLY</td>
<td>10</td>
</tr>
<tr>
<td>1.3.1 APPLICATIONS OF LOW MOLECULAR WEIGHT GELATORS</td>
<td>15</td>
</tr>
<tr>
<td>1.3.2 CARBOHYDRATE BASED LMWGS</td>
<td>16</td>
</tr>
<tr>
<td>1.3.3 BUILDING BLOCKS WITH PHOTOCHEMICAL PROPERTIES</td>
<td>20</td>
</tr>
<tr>
<td>1.3.4 COMPOUNDS CONTAINING ISOXAZOLE FUNCTIONAL GROUP</td>
<td>28</td>
</tr>
<tr>
<td><strong>2. SYNTHESIS AND CHARACTERIZATION OF N-ACETYL-GLUCOSAMINE BASED MACROCYCLES</strong></td>
<td>33</td>
</tr>
<tr>
<td>2.1 INTRODUCTION</td>
<td>33</td>
</tr>
<tr>
<td>2.2 RESULTS AND DISCUSSIONS</td>
<td>35</td>
</tr>
<tr>
<td>2.3 CONCLUSION</td>
<td>62</td>
</tr>
<tr>
<td>2.4 EXPERIMENTAL SECTION</td>
<td>62</td>
</tr>
<tr>
<td><strong>3. SYNTHESIS AND CHARACTERIZATION OF PHOTO RESPONSIVE MOLECULES</strong></td>
<td>91</td>
</tr>
<tr>
<td>3.1 INTRODUCTION</td>
<td>91</td>
</tr>
<tr>
<td>3.2 RESULTS AND DISCUSSIONS</td>
<td>96</td>
</tr>
<tr>
<td>3.3 CONCLUSION</td>
<td>115</td>
</tr>
<tr>
<td>3.4 EXPERIMENTAL SECTION</td>
<td>115</td>
</tr>
<tr>
<td><strong>4. SYNTHESIS AND CHARACTERIZATION OF ISOXAZOLES BASED SUGAR DERIVATIVES</strong></td>
<td>130</td>
</tr>
<tr>
<td>4.1 INTRODUCTION</td>
<td>130</td>
</tr>
<tr>
<td>4.2 RESULTS AND DISCUSSIONS</td>
<td>133</td>
</tr>
<tr>
<td>4.3 CONCLUSION</td>
<td>146</td>
</tr>
<tr>
<td>4.4 EXPERIMENTAL SECTION</td>
<td>146</td>
</tr>
<tr>
<td><strong>5. CONCLUSIONS AND FUTURE RESEARCH</strong></td>
<td>158</td>
</tr>
<tr>
<td>5.1 CONCLUSIONS</td>
<td>158</td>
</tr>
<tr>
<td>5.2 FUTURE RESEARCH</td>
<td>162</td>
</tr>
</tbody>
</table>
REFERENCES ........................................................................................................................................164

APPENDICES
   A. LIST OF SAMPLES ................................................................................................................175
   B. COPYRIGHT PERMISSION .................................................................................................176

VITA ......................................................................................................................................................178
<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Excitation and emission wavelength of derivatives of <strong>CDG</strong></td>
<td>27</td>
</tr>
<tr>
<td>2. Macrolactonization of the intermediate 29 using different bases</td>
<td>41</td>
</tr>
<tr>
<td>3. Effect of the macrocycle on catalyzing the click chemistry using phenyl acetylene</td>
<td>53</td>
</tr>
<tr>
<td>4. Gelation results for coumarin glycoconjugates</td>
<td>102</td>
</tr>
<tr>
<td>5. Photophysical properties of coumarins and their glycoconjugates</td>
<td>105</td>
</tr>
<tr>
<td>6. Gelation results for coumarin based carbohydrate</td>
<td>138</td>
</tr>
</tbody>
</table>
**LIST OF FIGURES**

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Example of different types of saccharides</td>
<td>1</td>
</tr>
<tr>
<td>2. Examples of macrocycles</td>
<td>3</td>
</tr>
<tr>
<td>3. Structure of macrocycles with biological activity</td>
<td>4</td>
</tr>
<tr>
<td>4. Ring closing reactions</td>
<td>5</td>
</tr>
<tr>
<td>5. Ring closure by Diels-Alder reaction</td>
<td>6</td>
</tr>
<tr>
<td>6. Macrocyclization strategies for the preparation of Riccardin C</td>
<td>6</td>
</tr>
<tr>
<td>7. Synthetic strategies to obtain lactam-based macrocycle</td>
<td>7</td>
</tr>
<tr>
<td>8. (A) Huisgen’s cycloaddition reaction, (B) Sharpless’s CuAAC reaction</td>
<td>8</td>
</tr>
<tr>
<td>9. Structures of macrolactone exhibiting biological activity</td>
<td>9</td>
</tr>
<tr>
<td>10. Classification of gels</td>
<td>11</td>
</tr>
<tr>
<td>11. Different groups contributing to non-covalent interactions</td>
<td>12</td>
</tr>
<tr>
<td>12. Schematic representation for the primary, secondary, and tertiary structure of the gelation process</td>
<td>13</td>
</tr>
<tr>
<td>13. Dye release by photo-responsive hydrogel (PR-Hgel)</td>
<td>15</td>
</tr>
<tr>
<td>14. L-proline based gelators for catalysis</td>
<td>16</td>
</tr>
<tr>
<td>15. Glucose showing multiple hydroxyl groups</td>
<td>16</td>
</tr>
<tr>
<td>16. Molecular structure of amide, carbamate, amide linked triazolyl derivatives</td>
<td>17</td>
</tr>
<tr>
<td>17. Study of different protecting group effect. (a) p-methoxy benzylidene acetal protected groups, (b) 2-phenylethylidene acetal protected groups</td>
<td>18</td>
</tr>
<tr>
<td>18. (A) β anomers with triazole linked derivatives, (B) peracetylated disaccharide triazole derivatives</td>
<td>20</td>
</tr>
<tr>
<td>19. Commonly used fluorophores (A) TPE (B) PDI (C) NI (D) BODIPY</td>
<td>22</td>
</tr>
<tr>
<td>20. Structure and derivatives of coumarin for therapeutic application</td>
<td>23</td>
</tr>
<tr>
<td>Figure</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>21. Structure of a coumarin-dipeptide gelator</td>
<td>24</td>
</tr>
<tr>
<td>22. Resonating structure of coumarins with different substituents</td>
<td>25</td>
</tr>
<tr>
<td>23. Fluorescent spectra of compound 1 and its derivatives</td>
<td>26</td>
</tr>
<tr>
<td>24. Photo triggerable gelator precursor releasing the supramolecular gelator</td>
<td>28</td>
</tr>
<tr>
<td>25. Isoxazole based drugs</td>
<td>29</td>
</tr>
<tr>
<td>26. Isoxazole prepared by intramolecular oxidative cyclization</td>
<td>30</td>
</tr>
<tr>
<td>27. Isoxazole formed at different position of sugar derivatives</td>
<td>31</td>
</tr>
<tr>
<td>28. Isoxazole linked indole C-glycopyranosides</td>
<td>31</td>
</tr>
<tr>
<td>29. Preparation of isoxazole based low molecular weight gelators</td>
<td>32</td>
</tr>
<tr>
<td>30. Structures of sugar-based macrocycles 1-4</td>
<td>34</td>
</tr>
<tr>
<td>31. $^1$H NMR spectra of LM28 with different amount of TBACl from 0.0 to 10.0 equivalents</td>
<td>43</td>
</tr>
<tr>
<td>32. $^1$H NMR spectra of LM28 showing merged Hb and Hc with different amount of TBACl</td>
<td>44</td>
</tr>
<tr>
<td>33. Possible binding of chlorine ion with different protons of macrocycle DLM28 and $^1$H NMR spectra of DLM28 with different amount of TBACl from 0.0 to 5.0 equivalents</td>
<td>45</td>
</tr>
<tr>
<td>34. $^1$H NMR spectra of DM35 with different amount of TBACl from 0.0 to 5.0 equivalents</td>
<td>46</td>
</tr>
<tr>
<td>35. Possible binding of chloride ion with different protons of macrocycle C2ML and $^1$H NMR spectra of C2ML at different concentration of TBACl</td>
<td>47</td>
</tr>
<tr>
<td>36. $^1$H NMR spectra of C2DML with different amount of TBACl from 0.0 to 10.0 equivalents</td>
<td>48</td>
</tr>
<tr>
<td>37. $^1$H NMR spectra of LM28 with different amount of TBABr from 0.0 to 5.0 equivalents</td>
<td>49</td>
</tr>
<tr>
<td>38. $^1$H NMR spectra of LM28 with different amount of TBAI from 0.0 to 5.0 equivalents</td>
<td>50</td>
</tr>
<tr>
<td>39. $^1$H NMR spectra of DM35 with different amount of TBABr from 0.0 to 5.0 equivalents</td>
<td>51</td>
</tr>
<tr>
<td>40. $^1$H NMR spectra of DM35 with different amount of TBAI from 0.0 to 5.0 equivalents</td>
<td>51</td>
</tr>
<tr>
<td>41. $^1$H NMR and $^{13}$C NMR spectra of compound 7c in CDCl$_3$</td>
<td>55</td>
</tr>
<tr>
<td>Figure</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>42. $^1$H NMR and $^{13}$C NMR spectra of compound 9c (LM28) in CDCl$_3$</td>
<td>56</td>
</tr>
<tr>
<td>43. $^1$H NMR and $^{13}$C NMR spectra of compound DM35</td>
<td>57</td>
</tr>
<tr>
<td>44. $^1$H NMR and $^{13}$C NMR spectra of compound DLM28</td>
<td>58</td>
</tr>
<tr>
<td>45. COSY and HSQC NMR spectra of LM28</td>
<td>59</td>
</tr>
<tr>
<td>46. IR spectra of compound DM35 and DLM28</td>
<td>60</td>
</tr>
<tr>
<td>47. HRMS spectra of compound DM35 and DLM28</td>
<td>61</td>
</tr>
<tr>
<td>48. Example of photochromic units</td>
<td>91</td>
</tr>
<tr>
<td>49. Structures of coumarin derivatives for pharmacological application</td>
<td>92</td>
</tr>
<tr>
<td>50. Synthesis of triazolyl coumarins</td>
<td>94</td>
</tr>
<tr>
<td>51. Diarylethene based LMWGs</td>
<td>95</td>
</tr>
<tr>
<td>52. Structures of different coumarin intermediates</td>
<td>97</td>
</tr>
<tr>
<td>53. Photos for the gels formed by compound 27 in DMSO: H$_2$O (1:2) with 3.3 mg/mL; (A) Image of gel under natural light, (B) under UV (320 nm) light, (C) optical micrograph of coumarin derivative 27 (scale bar; 50 μm)</td>
<td>103</td>
</tr>
<tr>
<td>54. Gels photos of compound 36 in EtOH with 5.0 mg/mL; (A) Image of gel under natural light, (B) under UV (320 nm) light</td>
<td>104</td>
</tr>
<tr>
<td>55. Fluorescent spectra of compounds 14 and 27, the $\lambda_{ex} = 324$ nm</td>
<td>106</td>
</tr>
<tr>
<td>56. Fluorescent spectra of compounds 17 and 24, the $\lambda_{ex} = 290$ nm</td>
<td>106</td>
</tr>
<tr>
<td>57. Fluorescent spectra of compounds 20 and 36, the $\lambda_{ex} = 346$ nm</td>
<td>107</td>
</tr>
<tr>
<td>58. $^1$H NMR and $^{13}$C NMR spectra of compound 18 in d$_6$-DMSO</td>
<td>110</td>
</tr>
<tr>
<td>59. $^1$H NMR and $^{13}$C NMR spectra of compound 27 in d$_6$-DMSO</td>
<td>111</td>
</tr>
<tr>
<td>60. $^1$H NMR and $^{13}$C NMR spectra of compound 36 in CDCl$_3$</td>
<td>112</td>
</tr>
<tr>
<td>61. $^1$H NMR and $^{13}$C NMR spectra of compound 42 in d$_6$-DMSO</td>
<td>113</td>
</tr>
<tr>
<td>62. IR spectra of compound 27 and 36</td>
<td>114</td>
</tr>
</tbody>
</table>
63. Structures of isoxazoles based molecules with biological activity .............................................131

64. Design rational of isooxazole based glycoconjugates ..................................................................133

65. Pictures of gels formed by isooxazole derivatives. (A) compound 13a in EtOH: H2O (v/v 1:2) at 5.0 mg/mL; (B) compound 13a in H2O at 2.0 mg/mL ........................................139

66. Gel column for the dye absorption experiment. (A) Gel column before the experiment, (B) Column after loading with 2 mL of 23.9 µM toluidine blue solution, (C) Toluidine blue solution (2.1 mL) collected after passed through the column .........................140

67. The UV-Vis spectra of 23.9 µM toluidine blue solution (Standard) before the experiment and after the experiment (Expt). ..................................................................................................................140

68. 1H NMR and 13C NMR spectra of compound 13a in CDCl3 .............................................................141

69. 1H NMR and 13C NMR spectra of compound 13c in CDCl3 .............................................................142

70. HSQC (top) and COSY (bottom) NMR spectra of compound 13a in CDCl3 .................................143

71. HSQC (top) and COSY (bottom) NMR spectra of compound 13c in CDCl3 .................................144

72. IR spectra of compound 13a and 13c .............................................................................................145

73. Synthesis of macrocycles, photo responsive molecules and isoxazole based glucosamine from N-acetyl-D-glucosamine ..............................................................................................................158

74. Macrocycles showing binding properties with tetrabutylammonium halides ...............................159

75. Coumarin and its glycoconjugate with different fluorescence properties ........................................160

76. Isoxazole based glycoconjugates (C1 and C2 positions) ..................................................................161
CHAPTER 1
BACKGROUND AND LITERATURE REVIEW

1.1 INTRODUCTION

Carbohydrates are biological molecules which consist of carbon (C), hydrogen (H) and oxygen (O) in their molecular formula, represented by the general formula of \((\text{CH}_2\text{O})_n\). Based on their chemical structures and hydrolysis products, carbohydrates can be classified into four major subclasses: monosaccharides, disaccharides, oligosaccharides, and polysaccharides. If the molecule cannot be hydrolyzed into more than one sugar unit, it is called monosaccharide. If the molecule can be hydrolyzed and form two saccharides, then it is called disaccharide. Carbohydrates that can be hydrolyzed to produce a few monosaccharide units (from 2 to 20) are termed oligosaccharides. As shown in Figure 1, glucose is an example of monosaccharide and sucrose is a disaccharide. If the molecule consists of many saccharide units, then it is called as polysaccharides, for example amylose.

![Figure 1. Examples of different types of saccharides.](image-url)
If these carbohydrates are linked covalently to other species such as proteins, peptides, lipids, or other functional groups, they are termed glycoconjugates. Biologically occurring glycoconjugates are essential compounds involved in cellular interactions including cell-cell recognition and cell-matrix interactions.3

There are several advantages to develop new glycoconjugates from carbohydrate starting materials for further functionalization, including the fact that they are bioavailable, structure diverse, and readily available. In this research, several different classes of organic compounds were synthesized and studied. The first topic (Chapter 2) focused on carbohydrate-based macrocyclic compounds. The synthesis of glucosamine-based macrocycles from cyclization of C1 to C6 positions and C2 to C6 positions will be discussed. The applications of these novel macrocycles were also studied, including their uses as host ligands for the entrapment of ions. The second main project (Chapter 3) will focus on photo responsive materials, which include two main subclasses of compounds. The synthesis of different glycoconjugates linked with coumarins and their gelation behavior, and photophysical properties will be discussed first, followed by photo-responsive diarylethene derivatives. In Chapter 4, a series of isoxazole based glycoconjugates are synthesized and analyzed. The molecular self-assembling and gelation properties of these derivatives are analyzed and summarized.

1.2 INTRODUCTION OF MACROCYCLES

In general, macrocycles can be defined as the molecules or ions containing twelve or more membered rings. Some examples of macrocycles are, crown ethers,4 calixarenes,5 porphyrins,6 cyclodextrins,7 etc. Figure 2 shows two examples of macrocycles. The crown ether, 18-crown-6, is a macrocyclic with 18 membered ring and six oxygen atoms in the molecule, hence the name
18-crown-6. Charles J. Pederson shared Novel prize in Chemistry in 1987 for his work on crown ethers. Another example is Uroporphyrinogen III, an intermediate of heme. Heme has a porphyrin core. The metal complexes of porphyrins are found in nature, which play important biological functions, examples including iron containing hemoglobin and myoglobin.

Erythromycin (Figure 2) is a carbohydrate containing macrocycle which was found in nature as an antibiotic, it is known for the treatment of variety of infections like respiratory tract infection, skin infection, syphilis, and also used in newborns as ointments to prevent eye infection. Erythromycin is naturally occurring macrocycle first isolated from Saccharopolyspora erythraea in 1952. Erythromycins fall under macrocycle category as they contain more than 12-membered ring. Along with being a macrocycle, some other features of this macrocycle are; hetero atoms present in the ring, lactone functional group present in the ring and two different sugars attached with the macrocycle.

Figure 2. Examples of macrocycles.
Koblan’s group in early 2000s has reported that macrocyclic compounds showed significant increase in potency while in cyclic form, as shown in Figure 3. The farnesyltransferase inhibitor B (Figure 3B) has IC₅₀ values much lower than the corresponding open chain analogs. Compound B was found to be 20-fold more potent than its open chain inhibitor compound A, and also 55,000-fold more potent than its open chain analogue compound C.¹²

![Figure 3. Structures of macrocycles with biological activity.](image)

### 1.2.1 METHODS OF MACROCYCLE SYNTHESIS

The ring closing step is the most important step for macrocycle synthesis. There are a variety of methods for ring formation. In organic synthesis, this is called a ring-closing step. Some of ring closing methods are: azide-alkyne cycloaddition reaction,¹³ Diels-Alder reaction,¹⁴ Fischer indole synthesis,¹⁵ ring-closing metathesis,¹⁶ Robinson annulation,¹⁷ and Skraup reaction.¹⁸ As shown in Figure 4, these are general ring closing synthetic methods which are usually applied for the synthesis of smaller rings. Reactions such as azide-alkyne cycloaddition,¹⁹ Diels-Alder reaction²⁰ and olefin ring-closing metathesis²¹ can also be used for synthesis of macrocycles.
In 2005, Sorensen’s group utilized the intramolecular Diels-Alder reaction for the synthesis of Abyssomicin (Figure 5).\(^{22}\) Another example is shown in Figure 6, Riccardin C has been used by Kostiuk’s group in 2012 to show the multiple synthetic strategies for the formation of macrocyclic ring. The strategies shows how combination of different synthetic approaches like Wurtz, Wittig, McMurry and cross-coupling with Pd(0) can be utilized to build up the macrocyclic structures.\(^{23}\)
Fitzgerald’s group in 2012 studied two different approaches to synthesize 12-membered macrolactam (Figure 7). The first approach utilized $S_N$Ar reaction to obtain the final macrocyclization, under optimized condition the yield was in the range of 25-45%, however, in
the second approach, macrolactamization was utilized to afford the product in much improved yield of 83%. This example demonstrates the importance of synthetic routes for macrocycle synthesis.

![Synthetic strategies to obtain lactam-based macrocycle](image)

Figure 7. Synthetic strategies to obtain lactam-based macrocycle.

Azide-alkyne cycloaddition reaction is another popular tool for the cyclization step. The azide-alkyne reaction itself produces a five-membered 1,2,3-triazole ring. Triazoles are accepted for their characteristic properties of specificity and biocompatibility. Huisgen first studied this azide-alkyne cycloaddition reaction under thermal condition to give two of the isomers; 1,4-disubstituted triazole and 1,5-disubstituted triazole (Figure 8a). Under thermal condition, this cycloaddition reaction was not regioselective. Later, Sharpless and co-workers found that this
reaction can be accelerated by copper catalyst at room temperature and only one isomer, the 1,4-disubstituted triazoles were obtained exclusively (Figure 8b). This was coined the term as “Click” reaction and abbreviated this reaction as Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC). 

![Chemical Reaction Diagram]

Figure 8. (A) Huisgen’s cycloaddition reaction, (B) Sharpless’s CuAAC reaction.

### 1.2.2 CARBOHYDRATE-BASED MACROCYCLES

Carbohydrate-based macrocycles have found widespread and diverse applications such as building blocks in supramolecular chemistry, drug carrier systems, targets for drug discovery, and molecular recognition. There are both naturally occurring and synthetic macrocycles which contain macrolactone functional groups and are biologically active. This class of macrocycles with macrolactone functional groups has also shown its application in molecular recognition.
Recent study shows that the sugar-based macrocyclic compounds containing triazole moiety has the capability of binding to the guest molecule.\textsuperscript{30} The bis-triazole containing sugar-based macrocycle was synthesized by template assisted click reaction. S-phenyl ethyl ammonium salt was used as template for this reaction. Without this template, the reaction was very slow giving only 6\% yield. The improvement of yield after using template is believed to be due to the pre-organization of azide and alkyne precursors. This macrocyclic guest complex also discriminates between D- and L-phenylalanine, showing only interaction with L-phenylalanine.\textsuperscript{30}

Figure 9\textsuperscript{31} shows the structure of Ipomoeassin F and Glucolipsin A. Ipomoeassin F is disaccharide-based macrolactone, which exhibit anticancer properties and is also a potential protein-translocation inhibitor.\textsuperscript{32} Glucolipsin A is another macrocycle which contains two lactones functional groups, which inhibits specific phosphatases Cdc25A.\textsuperscript{33}
Macrocycles containing triazole moieties have been utilized due to their structural feature in pharmaceuticals.\textsuperscript{34} The triazole containing compounds usually accelerates rate of click reactions due to their basicity, multidenticity or their coordination lability.\textsuperscript{35} Triazole-based macrocycles have been utilized to accelerate the Cu (I) catalyzed azide-alkyne cycloaddition reactions (CuAAC).\textsuperscript{36} The macrocycles with 1,4-disubstituted triazole have been used as a ligand for ion recognition and host-guest complexes.\textsuperscript{37}

1.3 MOLECULAR SELF-ASSEMBLY

Molecular self-assembly can be defined as the assembly without guidance or management from an external source.\textsuperscript{38} In biological systems, self-assembly leads to the construction of micelles, vesicles, fibers, and supramolecular gels. Our research mainly focuses on supramolecular gels. Supramolecular gels are the solid-like materials formed by intermolecular interactions between the molecules.\textsuperscript{39} Apart from supramolecular gels, there is macromolecular gel as well. The difference between these gels arises from the classification of the gels. The simple classification of gels is shown in Figure 10.\textsuperscript{40}

Gels can be classified by two different ways, according to their source or according to the medium in which these gels are prepared.\textsuperscript{40} By source, they can be either natural or artificial. Artificial gels which can further be divided into supramolecular gels or macromolecular gels. Macromolecular gels can occur in two different ways where the molecules crosslink together by the chemical process forming the covalent bond. In-between these crosslinks, there might be the presence of physical interactions. On the other hand, supramolecular gels are solely formed by physical interactions through non-covalent forces. Wang’s group has been working on the design and synthesis of supramolecular gelators.\textsuperscript{41-43} These gels can also be prepared using different
solvents and can be classified accordingly. If they are prepared in water as a solvent, they are called hydrogels. If organic solvents are used in the preparation of gels, the resulting gels are called organogels. After removing solvent from these gels, the residues are called xerogels. Aerogels are formed when the solvent used to prepare the gel is replaced by other gas.\textsuperscript{40}

Supramolecular gelators are organic compounds with a molecular weight of less than 2000 Da, which show gelation behavior in organic solvents and water. The intermolecular interaction leads to the formation of gels.\textsuperscript{44} These interactions are non-covalent interactions such as hydrogen bonding, hydrophobic forces, Van der Walls forces, \(
p-\pi\) interactions, and in some cases, halogen
bonding occurs as well. Figure 11 shows an example of how different functional groups can participate in different types of interactions.\textsuperscript{45}

![Diagram of non-covalent interactions](image)

**Figure 11.** Different groups contributing to non-covalent interactions.

The gelation process usually follows by the formation of three different levels of structures: primary, secondary, and tertiary structures. The primary step is just the molecular interaction or the non-covalent interactions. The molecular interactions build up the fibers-like structure, which is the secondary structure of the gel formation. Finally, these fibers entangle, giving the network-like structures that entrap the solvent in the matrix, giving the gel-like material. This whole process of gelation is schematically represented in Figure 12.\textsuperscript{46}
This self-assembly is affected by different factors like shear stress, pH, temperature, enzymes, and light. These factors can also be called physical stimuli in which the self-assembled molecules respond to these stimuli and change their properties. Factors like temperature help transition from gel to the solution (sol) and solution to gel. Usually, while increasing temperatures, the gel is converted to the solution, and decreasing temperature changes the solution back to the gel. The gelation process is thermoreversible. Due to the thermo-responsive behavior of the gel, the swelling and shrinking behavior might also be observed while the temperature surrounding the solvent changes. Different pH can be used to change the properties of the gels as well. The molecules can be prepared by acid or base sensitive groups, which can be triggered by changing the pH of the medium. Electro-responsive hydrogels have applications in biosensors and tissue engineering as bacterial cells can have electrolytic properties. The idea arises from the capability of these gels, which can respond towards the electrical field. If these gels prepared has different electrolytes, then they tend to be sensitive to electric current. Light-responsive gels are molecules
that can change their properties when the light of a different wavelength is irradiated to the system. Due to ease of use of light and high accuracy of delivery method, light-responsive supramolecular gels have more significant advantages over other stimuli-responsive techniques.

Photoresponsive systems can be used for the transition from sol-gel and vice versa.\textsuperscript{51} This transition leads to various applications of light-responsive systems in optical switches as well as drug delivery system.\textsuperscript{52,53} Use of the ultraviolet (UV) light can be utilized in the swollen and shrinking properties of the different hydrogelators. One of the examples by Rastogi’s group in 2017 shows the release of Alexa Fluor 750 dye (AF\textsubscript{750}) by the photo-responsive method (Figure 13). The photo-responsive hydrogel is prepared by polyethylene coupled with azobenzene. The gel molecules trap the AF\textsubscript{750} dye, where the gel structure consists of the trans-azobenzene moiety. Upon irradiation of UV light of 360 nm, the trans-azobenzene isomerizes to cis-azobenzene. This process leads to the shrinkage of the gel, which helps in the release of the dye molecule.\textsuperscript{54} Other stimuli-responsive systems can be pressure-responsive,\textsuperscript{55} magnetic-responsive,\textsuperscript{56} ultrasound-responsive.\textsuperscript{57}
1.3.1 APPLICATIONS OF LOW MOLECULAR WEIGHT GELATORS (LMWGS)

There are a variety of applications of LMWGs and supramolecular gels. Some applications include biomedicine, enzyme immobilization, electronics, water purification, tissue engineering, drug delivery, and organocatalysis. A phase-selective gelator for oil-spill remediation has been developed. This method involves mixing N-methyl acetamide and lauric acid in a deep eutectic solvent (DES). This process gives a novel gelator that selectively gels with oil only. LMWGs can be used in the drug delivery systems by developing the compound that can perform as a prodrug and form a hydrogel. Different factors can further trigger this hydrogel to release the drug. Also, in some LMWGs, which contain a high density of catalytic sites on their surface, the fibrous network of these gels can perform as a better catalyst. In 2009, Rodriguez's group designed...
L-proline based gelator (Figure 14) for catalysis. The gelation of catalysts controls the products, whereas in solution the yield was low.\textsuperscript{61}

Figure 14. L-proline based gelator for catalysis.

1.3.2 CARBOHYDRATE BASED LMWGS

Carbohydrates are one of the easily obtained natural substances widely used for the preparation of LMWGs. Figure 15 shows the structure of the glucose molecule, a typical example of a monosaccharide.

Figure 15. Glucose showing multiple hydroxyl groups.
Some of the advantages of using carbohydrates as LMWGs are their abundance in nature and they can be obtained from renewable natural resources. They also have multiple chiral centers in the molecule, which can be used for enantioselective reactions. The multiple hydroxyl groups in the carbohydrates can be utilized as hydrogen bond donors and acceptors. These hydroxyls can be easily functionalized to give a new functional group with different properties. Carbohydrate based LMWGs could be used in the human body potentially without any harmful side effects. In other words, they are biocompatible.

Wang group has reported numerous carbohydrates based LMWGs, including glucose, galactose, and glucosamine, as the building block. These building blocks undergo synthetic processes like glycosylation, protection/deprotection, and functionalization to obtain desired derivatives. Some of the derivatives are amides, carbamates, triazoles, etc. shown in Figure 16.

![Molecular structure of amide, carbamate, amide linked triazolyl derivatives.](image-url)
The examples in Figure 17 were all derivatized at C2 carbon, where different functional groups were used to form the final products. The comparative studies between different R groups in these amide and carbamate derivatives have been demonstrated. The amide-linked triazolyl derivatives have also been studied to investigate the properties of triazole as a functional group. Triazole derivatives have also been studied for the different R substituents. Different R substituents are essential for controlled drug release. The amide-linked triazole derivatives also can be used for environmental remediation for dye absorption.42

Figure 17. Study of different protecting group effect. (A) p-methoxy benzylidene acetal protected groups, (B) 2-phenylethylidene acetal protected groups.
Utilizing different protecting groups at 4,6 positions, the gelation behavior of these derivatives was studied, shown in Figure 17. The pH-responsive gelators were obtained by amide derivative of \( p \)-methoxy benzylidene acetal protected groups, and the urea derivatives were utilized for the Naproxen sodium release study in different pH.\(^{42}\) The release of Naproxen was faster in acidic conditions compared to the neutral condition. A series of 4,6-\( O \)-(2-phenylethylidene)-D-glucosamine-based amides and urea’s were also studied for their gelation behavior. The long alkyl group containing amide derivatives was an effective gelator in pump oil and engine oils. Variable temperature studies were shown for amide and urea derivatives to support hydrogen bonding during gelation. The temperature studies were done using \(^1\)H NMR spectroscopy.\(^{45}\)

Apart from alpha (\( \alpha \)) anomers that are discussed, the Wang’s group has also worked on the beta (\( \beta \)) anomers (Figure 18A) where the glucose and glucosamine based triazole derivatives were synthesized as successful LMWGs.\(^{43,41}\) These derivatives successfully formed organogel and hydrogels, showing the significant effect of the triazole functional group in helping in the self-assembly. The triazole-linked derivatives were also extended towards disaccharides (Figure 18B). These disaccharides were investigated for their gelation behavior.\(^{66}\) The study showed that maltosyl triazoles were better gelators than lactosyl derivatives, which gives the information about how different configuration in some sugar leads to the formation of better gels whereas others do not.\(^{66}\)
Figure 18. (A) β anomers with triazole linked derivatives, (B) peracetylated disaccharide triazole derivatives.

1.3.3 BUILDING BLOCKS WITH PHOTOCHEMICAL PROPERTIES

Light-responsive molecules can change their properties when the light of another wavelength is irradiated to the system. If any substances can emit light after absorbing light or electromagnetic radiation, this phenomenon is known as fluorescence. These molecules are usually the fluorescent core or scaffolds. These scaffolds can be attached to the carbohydrate molecules to obtain photoresponsive glycoconjugates. These photoresponsive glycoconjugates can be applied to cancer cell imaging and detection of protein cells. These photoresponsive molecules can also be used towards the drug delivery application. Carbohydrates with different configurations tend to show selectivity towards different binding sites, which can be implemented to find the desired target.

There are a variety of fluorescent cores that can be used to prepare the glycoconjugates. Fluorescence is an easy and sensitive technique to implement, which has attracted research areas...
like environmental science, biochemistry as well as biomedicine.\textsuperscript{70,71} The design of fluorescent probes usually involves the “on-off” and “off-on” signaling, where these works to quench or reactivate when they interact with the analyte. Aggregation-induced emission has also found its application for fluorescent “off-on” probes used in biosensing and bioimaging. In aggregation-induced emission, the use of weak emitting fluorophores dramatically shows strong emission, as the intramolecular rotation and vibration are restricted due to aggregation.\textsuperscript{72,73} The use of different fluorophores while conjugated with carbohydrates gives structurally and functionally different fluorescent glycoconjugates.\textsuperscript{69} This can lead to the design of different probes with specific properties like solubility, emission at desired region to reduce biological background fluorescence and biocompatible molecules. Some of the widely used fluorescent probes are tetraphenylethylene (TPE, Figure 19A) which shows the enhanced fluorescence properties by aggregation.\textsuperscript{74} Perylenediimide (PDI, Figure 19B) is thermally and photochemically very stable and has very high quantum yields in water and organic solvents. 1,8-naphthalimide (NI, Figure 19C) are multifunctional fluorophores that are used in DNA targeting, cellular imaging agents and are believed to have potential anticancer activity. The ease of synthesis of NI from commercially available 1,8-naphthalic anhydrides and amine makes it readily available, and its diverse application has been actively studied.\textsuperscript{75,76,77} Boron-dipyrromethene (4,4-difluoro-4-bora-3a,4a-diaza-s-indacene, BODIPY, Figure 19D) is popular due to the emission wavelength range. The emission wavelength ranges from visible to near IR region by modification on their structures.\textsuperscript{78,79,80}
Figure 19. Commonly used fluorophores: (A) TPE (B) PDI (C) NI (D) BODIPY.

Apart from these, fluorescein, rhodamines, porphyrins, pyrenes, and coumarins are commonly used fluorophores. Coumarin derivatives possess different therapeutic applications for treating breast cancer, skin disorders, leukemia, and some show anticoagulation properties. Figure 20 shows the general structure of coumarin and some of the coumarins that have therapeutic applications.
Along with the therapeutic applications, coumarins show photochemical applications as well. In 2015 Draper’s group showed the photodimerization of a coumarin-dipeptide gelator (Figure 21). The researchers explained the possible stacking of the gelator molecules in the gel before and after irradiation with UV light of 365 nm. The study showed that gel strength increased significantly after being exposed to UV light, which suggests that the increased strength is probably due to the dimerization of the coumarin functional group. They showed that the clear gels become cloudy and turbid after being exposed to a UV light of 365 nm and the study was supported by scanning electron microscopy (SEM) images before and after irradiation with UV light. It was also further supported by gel's rheological properties, which showed increased viscous property upon irradiation.
The photochemical properties of coumarins depend on their extended resonance from the benzene ring. Substituted coumarins can show different absorbance radiations. Figure 22 shows the resonance hybrid structure (B) in 3-aldehyde based coumarin. The conjugation can be further extended by substituting different electron-withdrawing groups or donating groups like structure C. The methoxy group and dimethylamine as different substituents help in resonating structure by the lone pair of electrons in oxygen and nitrogen. Similarly, in the 3-position of coumarin, the amine can replace the oxygen (D) to give different substituents, which changes the absorption behavior of the coumarin.\textsuperscript{88}

Figure 21. Structure of a coumarin-dipeptide gelator.
In 2016 Yamamoto showed the use of different substituted coumarin linked with sugar.\textsuperscript{89} They synthesized fluorescent glucose tracer (Figure 23, 1) and its derivatives by utilizing C-N coupling reactions (Pd-catalyzed) between glucosamine and fluorescent probe. Fluorescent spectra of compound 1 and its derivatives are shown in Figure 23. It clearly shows that different substituents can help in the blue shift and red shift, as shown by the emission maxima of the different compounds summarized in table 1. The study with compound 1 showed that it was taken up by mouse insulinoma 6 (MIN6) cells through glucose transporters (GLUTs), which was previously shown with a different fluorescent probe.\textsuperscript{90,91}
Table 1. Excitation and emission wavelength of derivatives of \( \text{CDG} \).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Abbreviation</th>
<th>Excitation ((\lambda_{\text{ex}}, \text{nm}))</th>
<th>Emission ((\lambda_{\text{em}}, \text{nm}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{CDG} )</td>
<td>366</td>
<td>455</td>
</tr>
<tr>
<td>3</td>
<td>( 3\text{-MCDG} )</td>
<td>362</td>
<td>460</td>
</tr>
<tr>
<td>4</td>
<td>( 3\text{-TFMCDG} )</td>
<td>381</td>
<td>455</td>
</tr>
<tr>
<td>5</td>
<td>( 4\text{-MCDG} )</td>
<td>362</td>
<td>446</td>
</tr>
<tr>
<td>6</td>
<td>( 4\text{-TFMCDG} )</td>
<td>378</td>
<td>500</td>
</tr>
</tbody>
</table>

Compounds \(1, 2, 3, \) and \( 5 \) showed a blue shift compared to \(2\text{-}[\text{N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino}-2\text{-deoxy-D-glucose (2-NBDG). Compound 6 showed green fluorescence while using a different fluorescent probe with more extended conjugation showed red shift compared to 2-NBDG (540 nm).}

In 2016 Feng group synthesized galactose-based precursor for gelator with the coumarin as the fluorescent probe.\(^92\) The idea was to prepare the light-responsive system where the light will be used to trigger the gelation of the desired system. This precursor with the photocleavable site can be cleaved with the UV light of 320 nm. After cleavage, the hydrolyzed coumarin moiety can perform as a supramolecular gelator (Figure 24). This precursor was tested in a human liver cancer cell (HepG2) and successfully killed the cancer cell. The galactose moiety specifically targets the cancer cells and binds with the asialoglycoprotein receptor. The precursor is taken up by cells by receptor-mediated endocytosis. Upon irradiation by UV light, the precursor releases the hydrogelator, which is self-assembled to form a nanofiber-like structure that induces cell death. The nanofibers disturb the cytoskeleton of cells and cause apoptosis.\(^92\)
1.3.5 COMPOUNDS CONTAINING ISOXAZOLE FUNCTIONAL GROUP

Five membered heterocyclic rings containing isoxazoles are known as essential synthons.\textsuperscript{93} Isoxazoles show various antitumor, anticancer, antibacterial, and antifungal activities. This class of heterocycles (Figure 25) have been used for anti-inflammatory (A), anti-rheumatic (B), beta-lactamase resistant (C), and androgenic steroids as well (D).\textsuperscript{94}
The synthetic approaches of isoxazole attached to sugar moieties were reported with the use of α, β-unsaturated oximes. This product was achieved by intramolecular oxidative cyclization in the presence of iodine, potassium iodide, and sodium hydrogen carbonate (Figure 26). The reaction was completed in 4.0 h at 100 °C.
There have been studies for the development of isoxazole-based glycoconjugates with the use of terminal alkyne. Isoxazole ring can also be used for bioconjugation. This isoxazole ring has been utilized to make the sugar derivatives in different positions (C-1, C-3, C-5, and C-6), as shown in Figure 27. The synthesis of these glycoconjugates was done using 18-crown-6 as catalyst and K$_2$CO$_3$ as a base. The temperature of the reaction was 80 °C, and the reaction was completed in 8.0 h. The reaction time was decreased to a total of 15 minutes under microwave condition at 110 °C.\textsuperscript{94}
Another recent study has shown that isoxazole-linked indole glycopyranosides (Figure 28) showed the anticancer activity at the micromolar level (22.3 µM) in the breast cancer cell (MDA-MB-231). This compound was found more potent to MCF-7 (different cell line).  

Figure 28: Isoxazole linked indole C-glycopyranosides.
Isoxazole-based gelators have also been studied in recent work presented by Nandi’s group. These gels showed their excellent gelation properties and were able to separate bisphenol and oil spills from water. The ease of synthesis of these molecules simply from oximes with the use of sodium hypochlorite was straightforward to obtain desired isoxazole based products (Figure 29).96

Figure 29: Preparation of isoxazole based low molecular weight gelators.

Research in carbohydrate chemistry is in high demand due to its involvement in biological processes. Carbohydrates are one of the building blocks in supramolecular chemistry due to their ability to form many hydrogen bonds. Sugar based scaffolds have been used for preparation of organic macrocycles, nanomaterials, polymers, dendrimers as glycoconjugates. These glycoconjugates can be utilized for host-guest encapsulation, self-assembly and catalytic properties. Some of the synthetic challenges, catalytic properties, molecular self-assembly, application of gelators as drug delivery and environment remediation of N-acetyl D-glucosamine based sugar are discussed in this dissertation.
CHAPTER 2
SYNTHESIS AND CHARACTERIZATION OF N-ACETYL-GLUCOSAMINE BASED MACROCYCLES

Adapted from manuscript:
The content of this chapter is reprinted with permission from Adhikari, S. B.; Chen, A.; Wang, G., 2021. Synthesis of Carbohydrate Based Macrolactones and Their Applications as Receptors for Ion Recognition and Catalysis.31 2021, 21, 3994. The manuscript can be found online at https://doi.org/10.3390/molecules26113394 (Creative Commons CC BY 4.0 license)

2.1 INTRODUCTION

Sugar based macromolecular compounds are versatile due to their structural and functional properties and its molecular architectures. There are many natural as well as synthetic sugar based macrocycles which are applied for different applications in the field of drug development, molecular recognition and advanced functional materials.97-100 These macrocycles containing the lactone functional groups are important due to their potential biological activities101,102 and also used for the design of chemo sensors and other functional molecular assemblies.98,103,104 One of the macrocyclic lactones has been reported to show antioxidative activities.104 Some examples of macrocyclic compounds are shown in Figure 30. Compound 1 is a natural occurring glycomacrolactone isolated from medicinal plants.104 The synthetic glyco-macrocycle 2 has photochromic properties and the Z-isomer has improved thermal stability than other azobenzene derivatives.103,105 C2-symmetrical sugar based macrocycle 3 exhibits chiral recognition between L- and D-phenylalanine methyl ester hydrochlorides.30 This macrocycle 3 discriminates D-phenylalanine from L-phenylalanine.
These important properties are the driving forces for synthetic chemists for the further development and studies of the glycomacrocycles. The biggest challenges in macrocycle synthesis are to develop new strategies for the cyclization step. The methods for macrocyclization include synthetic approaches like olefin metathesis, Cu (I) catalyzed azide alkyne cycloaddition reactions (CuAAC) also known as “click chemistry”, nucleophilic displacement, Pd catalyzed cyclization and dialkyne Glaser coupling reactions. Click chemistry can be used as one of the approaches for the ring closing step where we can use different metal catalyst to obtain regioselective 1,2,3-triazole heterocyclic functional group.

One of the example of sugar based macrocycle containing this triazole moiety, as shown in Figure 30, macrocycles 3 are useful in forming host guest complexes. In our lab we have synthesized sugar based macrocycles 4 by click chemistry, which can accelerate the Cu mediated azide alkyne cycloaddition reactions.

Figure 30. Structures of sugar-based macrocycles 1-4.
We have shown the synthesis of non-symmetrical furanose based macrocycles by Cu (I) catalyzed alkyne azide cycloaddition reactions (CuAAC). We have implanted two triazoles in the macrocyclic ring by utilizing the click chemistry twice, once being the final step for the ring closure. These macrocycles with bis-triazole moieties are found to be effective ligands in accelerating the CuSO₄ mediated AAC reactions. The strategy for our previous synthesis was the utilization of intramolecular azide alkyne cycloaddition reaction as the last step of the ring formation, taking advantage of the flexibility of the alkyl chain, but also the reaction yields were only in 40-50%. The moderate yield for macrocyclization was due to the competition between cyclization with polymerization.

In this research, the main goal is to synthesize a new class of sugar-based macrocycles using an alternative strategy which may improve the overall synthetic yield. Two main objectives we are interested in synthesizing these macrolactones are that they may have biological activities and functions as enzyme inhibitors, second reason is easy access to a new class of catalyst or ligands for cycloaddition reactions.

2.2 RESULTS AND DISCUSSIONS

2.2.1 SYNTHESIS OF THE MACROLACTONE SERIES I

In this research, we have synthesized several sugar-based macrocycles using commercially available N-acetyl-D-glucosamine as the starting material. Intermediate 6 was synthesized from N-acetyl-D-glucosamine in four steps following our previous procedure. The acyclic precursors were synthesized using click chemistry from intermediate 6. Subsequently, ring-closing step furnishing the macrocycles was achieved by nucleophilic substitutions to obtain the macrolactones. The detailed syntheses are shown in Schemes 1-4. As shown in Scheme 1, the
benzoyl protected azido compounds 6 were prepared from N-acetyl-D-glucosamine 5 in three steps as previously reported by us. We made several acyclic precursors by reacting 6 with different alkynoic acids utilizing click reaction gave the carboxylic acids 7. Then an intramolecular nucleophilic substitution reaction was carried out using K$_2$CO$_3$ as the base in DMF at 75 °C to afford mono-triazole macrolactones 9a-9c, 10a-10c with different ring sizes. For the synthesis of bis-triazole based macrolactones, the same intermediates 6 were used. As shown in Scheme 2, reaction of 6 with triazole containing alkynoic acids using click chemistry gave the acyclic precursors 12, which then underwent intramolecular cyclization in the same manner to afford the desired macrocycles 14a-b and 15a-b in better yields.

Scheme 1. Synthesis of mono-triazole sugar linked macrocycles.
Scheme 2. Synthesis of bis-triazole linked sugar-based macrocycles.

For the cyclization step, different solvents were tested beside DMF. Acetonitrile gave the similar results while the yield being slightly lower. The synthesis of compound 9c gave 77% yield. The use of dilute condition for the cyclization step prevents from intermolecular cyclization. Other possibility for this effective intramolecular cyclization might be the template assisted cyclization. This is possible due to the presence of potassium ion which act as template and bring carboxylic acid group toward the tosyl leaving groups. Other bis-triazole based macrocycles were also synthesized using acetonitrile as the solvents, the reactions required longer time (typically overnight) to completion and the products were obtained in 71-78% yields. The yields when using acetonitrile as the solvent were slightly lower than when using DMF as the solvent and takes a
longer time for the cyclization step, but the advantage of using acetonitrile is its lower boiling point and ease of removal after the reaction.

Scheme 3. Macro lactonization using other sulfonates as leaving groups.
The leaving group effects were studied for the final step of cyclization. This method used different sulfonate leaving groups at 6-OH position, these are shown in Scheme 3. Use of aliphatic sulfonyl leaving groups was not tested such as mesylate are small groups and would not be selectivity towards 3, 4 and 6 positions. In addition, we wanted to attach use aromatic sulfonyl groups at this step for the better detection and isolation of these UV active groups by chromatographic techniques. The intermediate 18 was treated with different sulfonates, like 4-chlorobenzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, and 1-naphthyl sulfonyl chloride to afford the corresponding sulfonates in moderate yields. The 4-bromosulfone 19a was converted to the corresponding dibenzoate 20a followed by click reaction to the intermediate 21a. The last step gave both monomeric 9c and dimeric lactones 22, with the yield of 72% and 10% respectively. When 4-chlorobenzene sulfonyl chloride was used, the sulfonate was displaced by chloride during the benzoylation step, compound 20b was obtained in moderate yield directly from intermediate 19b. The final step after click reaction gave both monomer and dimer with 68% and 8% yield respectively. Using naphthyl sulfonate as leaving group, the benzoylation step only afforded mono-benzylation product, therefore this was not continued further to prepare the macrocycle. These results showed the most suitable leaving groups would be tosyl sulfonates with the final cyclization steps without any dimerization and also with better yields.

2.2.2. SYNTHESIS OF THE MACROLACTONE SERIES II

Apart from the previously discussed macrolactones prepared from anomeric position (C1 linked with C6 position, Scheme 4), C2 macrolactones have also been designed and synthesized as shown in scheme 4. Compound 23, previously reported azido intermediate was used as the starting material for the first step. Deprotection of 23, gave the triol derivative 24 which was further
tosylated and benzoylated in two steps to obtain 26. To obtain 26 from 24, stepwise tosylation in pyridine followed by benzoylation in pyridine was done at 0 °C to obtain the desired compound in good yield. 26 was then subjected to click reaction with different alkynoic acids to obtain the macrolactone precursor with mono and bis-triazoles in the systems. Click reaction of 26 with 10-undecynoic acid gave the 27 which under macrolactonization gave product 28 with one triazole functional group in the ring.

Click reaction of compound 26 with triazole containing alkynoic acid was also utilized to obtain 29 and 30. This intermediate 29 undergoes macrolactonization process to obtain 31 and its dimer as byproduct 33 with different bases. Another intermediate 30 under macrolactonization condition didn’t give the desired product. To analyze the formation of byproduct 33, different bases were used for the macrolactonization step to see the cationic effect on the reaction (Table 2). We found that using Cs$_2$CO$_3$ as base only gave dimer 33 whereas K$_2$CO$_3$ and Na$_2$CO$_3$ gave monomer 31 only.
Scheme 4. Macrolactonization from C2-position.

Table 2. Macrolactonization of the intermediate 29 using different bases

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amount 29 (mg)</th>
<th>Concentration (mM)</th>
<th>Base 2.0 equiv</th>
<th>DMF (mL)</th>
<th>Temp (°C)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cs₂CO₃</td>
<td>12</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>100</td>
<td>9.7</td>
<td>Cs₂CO₃</td>
<td>12</td>
<td>70</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>8.7</td>
<td>K₂CO₃</td>
<td>10</td>
<td>70</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>9.7</td>
<td>Na₂CO₃</td>
<td>12</td>
<td>70</td>
<td>83</td>
</tr>
</tbody>
</table>

[Table 2 continued in the next page]
2.2.3 ANION BINDING STUDIES OF THE MACROCYCLES WITH TETRABUTYL AMMONIUM HALIDES

There are evidence of anions binding shown by triazoles derivatives, which shows the binding of chloride ions with C-H bond of triazole ring.\textsuperscript{123,124} To understand the anion binding properties of these macrolactones several $^1$H NMR studies were done using CDCl$_3$ as solvent. The studies were done with three tetrabutylammonium halides (TBAX) which includes tetrabutylammonium chloride (TBACl), tetrabutylammonium bromide (TBABr) and tetrabutylammonium iodide (TBAI). The amount of these TBAX were from 1.0 equivalent (equiv.) to 10.0 equiv. The stacked $^1$H NMR shows the chemical shift with different equiv. of TBAX.

2.2.3.1 MACROLACTONE BINDING WITH TBACL

**LM28:** There was obvious change for the triazole proton (Ha) upon addition of TBACl. This proton moved downfield from 7.41 to 7.61 ppm. There is another strong NH shift from 5.92 to 6.51 ppm, this shows the strong hydrogen bonding with the chloride ion. Other signals like H1, H2 and H3 didn’t shift as significantly but there were small changes on these peaks which shows the binding property of the macrocycle **LM28** with chloride ion. This change of chemical shift is shown in Figure 31.
Another interesting change of peaks was observed while increasing the concentration of TBACl from 1.0 equiv. to 10.0 equiv. for protons Hb and Hc which appear separately as multiples behaving as diastereotopic protons. Without any TBACl, these two protons are separate but after addition of TBACl, these starts to come together and finally merge to become distinct triplet, shown in Figure 32.
Figure 32. $^1$H NMR spectra of LM28 showing merged Hb and Hc with different amount of TBACl. Adapted from (Molecules. 2021, 26, 3394) under the creative commons license.

**DLM28:** There was downfield shift in triazole proton upon addition of 1.0 and 2.0 equiv. of TBACl, whereas there was upfield shift while going from 2.0 to 3.0 equiv. After 5.0 equiv. of TBACl, the triazole proton was in its original chemical shift of 7.72 ppm. This pattern basically shows that the effect of chlorine ion was significant with two equivalents of TBACl which later disappeared after further addition of more chlorides. There is decent downfield shift of NH proton from 6.24 to 6.37 ppm. Anomeric proton also shifts upfield from 4.92 to 4.87 ppm. These chemical shifts have been represented in the Figure 33 with possible binding of chlorine ion with different protons of macrocycle.
Figure 33. Possible binding of chloride ion with different protons of macrocycle DLM28 and \(^1\)H NMR spectra of DLM28 with different amount of TBACl from 0.0 to 5.0 equivalents.

**DM35:** The TBACl binding study for DM35 was studied and shown in Figure 34. The triazole peaks initially shifted downfield with 2.0 equiv. of TBACl but it started to shift upfield after total of 5.0 equivalent of TBACl. The NH peak showed most significant downfield shift of 0.14 ppm whereas there was only 0.04 ppm upfield shift observed for anomeric peak.
Figure 34. $^1$H NMR spectra of DM35 with different amount of TBACl from 0.0 to 5.0 equivalents.

**C2ML**: There was significant shift of different protons for the compound C2ML, as shown in Figure 35. The triazole shifted downfield with the addition of 2.0 equiv. of TBACl whereas it started to shift upfield after further addition of TBACl. There was 0.19 ppm downfield shift of NH proton whereas small 0.07 ppm upfield shift of anomeric proton was observed. One of the very obvious shifts were observed for proton Hb and Hc. They appear to be separate doublets without any TBACl, with the presence of 10.0 equiv. of TBACl, both appear to merge and show up as
pseudo quartet. There are change in peaks for proton H₃ and H₄, they appear as multiplet without addition of TBACl, with addition of 10.0 equiv. of TBACl, it appears as a resolved pentet or two triplets merged together.

Figure 35. Possible binding of chloride ion with different protons of macrocycle C2ML and ¹H NMR spectra of C2ML at different concentration of TBACl. Adapted from (Molecules. 2021, 26, 3394) under the creative commons license.
Figure 36. $^1$H NMR spectra of C2DML with different amount of TBACl from 0.0 to 10.0 equivalents. Adapted from (Molecules. 2021, 26, 3394)$^{31}$ under the creative commons license.

**C2DML:** There was significant shift of different protons for C2DML, as shown in Figure 36. The triazoles Ha and Hb (7.49 and 7.37 ppm before addition of TBACl) shifted downfield with the addition of 1.0 equiv. of TBACl (7.59 and 7.40 ppm respectively). There was 0.31 ppm downfield shift of NH proton whereas small upfield shift of anomeric proton was observed. As in C2ML (C2 monotriazole), Hc and Hd, merged after addition of 10.0 equiv. of TBACl. They
appeared to be pseudo quartet without any TBACl. There is change in peaks for proton $H_3$ and $H_4$, they appear as multiplet without addition of TBACl, with addition of 10.0 equiv. of TBACl, it appears as separate triplets.

### 2.2.3.2 MACROLACTONE BINDING WITH TBABR AND TBAI

**LM28** showed similar patterns as those of TBACl. With TBABr, from 0-5 equiv., there was 0.1 ppm downfield shift for triazole, 0.19 ppm downfield shift for NH and 0.03 ppm upfield shift for anomeric proton. With TBAI, from 0-5 equiv., there was 0.03 ppm downfield shift for triazole, 0.06 ppm downfield shift for NH and 0.03 ppm upfield shift for anomeric proton (Figure 37 and 38).

![Figure 37. $^1$H NMR spectra of LM28 with different amount of TBABr from 0.0 to 5.0 equivalents.](image-url)
Figure 38. $^1$H NMR spectra of LM28 with different amount of TBAI from 0.0 to 5.0 equivalents.

DM35 also showed similar trend for the chemical shift of different protons like triazole, NH and anomeric peaks. These changes in chemical shifts were not as significant as in case of TBACl. From 0-5 equiv of TBABr and TBAI, anomeric proton both showed only 0.03 ppm upfield shift, NH showed 0.04 ppm and 0.01 ppm respectively. Both triazoles shifted downfield about 0.07 ppm for 0.1 equiv of TBABr whereas for TBAI, there was no significant chemical shift (Figure 39 and 40).
Figure 39. $^1$H NMR spectra of DM$_{35}$ with different amount of TBABr from 0.0 to 5.0 equivalents.

Figure 40. $^1$H NMR spectra of DM$_{35}$ with different amount of TBAI from 0.0 to 5.0 equivalents.
2.2.4 EFFECT OF MACROLACTONES AS LIGANDS FOR CUAAC REACTIONS

After these compounds were obtained, they were tested as ligands for copper sulfate mediated AAC reactions. We tested the ligand for variety of alkynes like, 1-octyne and phenyl acetylene \( p \)-t-butyl-phenyl acetylene which is bulkier than phenyl acetylene and 5-phenyl 1-pentyne or pent-4-yn-1-ylbenzene, which contain substituted aryl containing alky functionalization groups.

For phenyl acetylene, when using 2.5 mol% macrocycle as the ligand and copper sulfate as the metal salt (Table 3), we found that two bistriazole derivatives \textbf{DM25} and \textbf{DM35} were the most efficient, the click reaction reached full conversion within 5.0 h, this was followed by the monotriazole macrocycles \textbf{LM34, LM36, LM26}, these three reactions almost reached full conversions after 9 h. With the amount of the monotriazoles increased to 5.0 mol%, we found that the two mono triazoles \textbf{LM26} and \textbf{LM34} were both effective in catalyzing the reactions. The results indicated that both the montraizole derivative and bistraizole derivatives were effective for phenyl acetylene click reaction.
Table 3. Effect of the macrocycle on catalyzing the click chemistry using phenyl acetylene

<table>
<thead>
<tr>
<th>Entry</th>
<th>No.</th>
<th>Conversion (%) at 1 h</th>
<th>Conversion (%) at 2 h</th>
<th>Conversion (%) at 5 h</th>
<th>Conversion (%) at 9 h</th>
<th>Isolated Yields for 35</th>
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<tbody>
<tr>
<td>(a)</td>
<td>none</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>9a</td>
<td>38</td>
<td>50</td>
<td>51</td>
<td>68</td>
<td>70%</td>
</tr>
<tr>
<td>2</td>
<td>9b</td>
<td>57</td>
<td>61</td>
<td>78</td>
<td>85</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>9c</td>
<td>57</td>
<td>61</td>
<td>67</td>
<td>79</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>10a</td>
<td>55</td>
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<td>79</td>
<td>93</td>
<td>82%</td>
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<td>14a</td>
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<td>14b</td>
<td>68</td>
<td>84</td>
<td>100</td>
<td>-</td>
<td>92%</td>
</tr>
<tr>
<td>9</td>
<td>15a</td>
<td>53</td>
<td>60</td>
<td>61</td>
<td>65</td>
<td>-</td>
</tr>
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<td>12</td>
<td>33</td>
<td>-</td>
<td>27</td>
<td>56</td>
<td>79 (10 h)</td>
<td>-</td>
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</table>

When using 1-octyne as the substrates, the different macrocycles showed very different results under similar screening reactions. With 2.5 mol% moacrocycles, 1.2 eq. of 1-octyne and 0.1 eq of CuSO₄ only the DM34 was very effective at catalyzing the reaction reaching 93% conversion at 2h, the other macrocycles didn’t show improvement to the control experiments when no macrocycles were used. When increasing the 1-octyne from 1.2 to 1.5 equivalents, the reaction completed within 1 h in presence of 2.5 mol% of DM34, however none of the other mono-triazole
based macrocycles and the other three bistriazole base macrocycles were effective even when increasing their loading to 5.0 mol%. The experiments confirmed that the DM34 was particularly efficient at catalyzing the click reaction of 1-octyne.

For the reactions with 5-phenyl-1-pentyne, which is an aliphatic alkyne with an aryl substituent, the alkyne reacted with the sugar azide rapidly when using 0.1 equivalent of CuSO₄ at 30 °C. the reaction reached 100% conversion typically within 1-2 h. Several experiments were carried out to analyze the effect of the macrocycles with reduced copper loading.

For 4-t-butyl phenyl acetylene, using 0.1 eq of copper sulfate, the reactions were quite slow, only DM25 (2.5 mol%) and DM35 (2.5 mol%) helped the reaction to reach full conversion at 20 h; when using 0.2 eq. of CuSO₄, the DM25 (2.5 mol%) was effective for catalyzing the reaction reaching 100% conversion at 5 h, using 5.5 mol% of macrocycles, DM35 reached 98% conversion at 5h; DM34 and DM24 were not that effective, giving similar conversions to the control experiment.
2.2.5 SELECTED NMR SPECTRA, MASS AND HRMS SPECTRA

Figure 41. $^1$H NMR and $^{13}$C NMR spectra of compound 7c in CDCl$_3$. 
Figure 42. $^1$H NMR and $^{13}$C NMR spectra of compound 9c (LM28) in CDCl$_3$. 
Figure 43. $^1$H NMR and $^{13}$C NMR spectra of compound DM35.
Figure 44. $^1$H NMR and $^{13}$C NMR spectra of compound DLM28.
Figure 45. COSY and HSQC NMR spectra of **LM28**.
Figure 46. IR spectra of compound **DM35** and **DLM28**.
Figure 47. HRMS spectra of compound DM35 and DLM28.
2.3 CONCLUSIONS

We have synthesized several novel N-acetyl-D-glucosamine and triazole derived macrolactones. Utilizing intramolecular S_N2 reactions, the macrolactones were synthesized in short steps and high efficiency. The final step for ring closure was done in 10 mM concentrations affording the macrocycles in 76-90% yields. Fourteen macrolactones were synthesized, out of which eleven were cyclized from C1 to C6 and others from C2 to C6. The preliminary studies shows that these macrolactones showed significant binding properties with tetrabutylammonium halides. The chemical shift changes in \(^1\)H NMR showed the evidence of interaction between the anions and macrolactones. Several macrolactones could accelerate the rate of CuAAC reactions. In comparison, bis-triazole macrocycles were more efficient ligands for accelerating the AAC reactions than mono-triazole based macrolactones. Some of these bis-triazole based macrolactones were also selective towards different acetylenes. The methods developed for the ring closing steps can be applied to the synthesis of different carbohydrate-based macrocycles.

2.4 EXPERIMENTAL SECTION

2.4.1 GENERAL METHODS

All reactions were carried out under normal conditions (1 atm pressure, without catalyst unless otherwise mentioned, rt or heated with specified temperature), reagents and solvents were obtained from commercial suppliers from Sigma-Aldrich, VWR, and Fisher and used directly without any purifications. All reactions unless otherwise noted were carried out in oven dried glassware under nitrogen atmosphere. All purification was conducted by flash chromatography using 230-400 mesh silica gel with a gradient of solvent systems. Thin-layer chromatography (TLC) analysis was performed with aluminum backed TLC plates (Sigma-Aldrich) with UV and
fluorescence indicator and visualized using UV lamp at 254 nm then stained with phosphomolybdic acid (PMA) solution. $^1$H NMR and proton-decoupled $^{13}$C NMR spectra were obtained with Bruker 400 MHz spectrometers in DMSO-$d_6$ or CDCl$_3$. The chemical shifts were reported using CDCl$_3$/DMSO-$d_6$ as internal standard at 7.26/2.50 ppm and at 77.0/39.5 ppm, respectively. 2D NMR experiments (HSQC, COSY) were also conducted to assist the compound characterizations. Some of the selected spectra for $^1$H NMR, $^{13}$C NMR, HSQC, COSY is shown in Figure 41, 43, 44 and 45. COSY spectra were used for characterizing the sugar protons as they usually appear between 3-5 ppm. After characterizing each proton, HSQC can be used to characterize the carbon NMR spectra. Figure 45 shows some correlation of sugar protons for LM28. Melting point measurements were carried out using a Fisher Jones melting point apparatus.

The molecular mass was measured using LC-MS on an Agilent 6120B Single Quad Mass Spectrometer and LC1260 system along with Shimadzu LCMS-2020. HRMS data (Figure 47) were obtained using positive electrospray ionization on a Bruker 12T APEX-Qe FTICR-MS with an Apollo II ion source.

**Synthesis of compound 2:**$^{125,126}$ N-acetyl-D-glucosamine 1 (5.0 g, 22.6 mmol, 1.0 equiv) was added to a 100 mL round bottomed flask (RBF) with 2-chloroethanol (7.75 mL, 113.05 mmol, 5.0 equiv) and BF$_3$•Et$_2$O (0.71 mL, 5.65 mmol, 0.25 equiv). The reaction mixture was stirred at 85 ºC for 4 h. The heating was turned off and the mixture was cooled room temperature. The mixture was then treated with water (15 mL) and washed with DCM (20 mL x 2) to remove excess 2-chloroethanol. The aqueous layer was then collected and evaporated. The crude product was obtained as dark brown oily crude. It was then dissolved in MeOH and coated on to SiO$_2$ (dry loading) for purification. The crude was then purified by chromatography on silica gel using a gradient of dichloromethane (DCM) and methanol from pure DCM to up to 10% MeOH/DCM ($R_f$
= 0.13 in 10% MeOH/DCM). The desired product was obtained as a white solid (4.01 g, 63%). $^1$H NMR (400 MHz, D$_2$O + 1 drop MeOH) $\delta$ 4.91 (d, $J$ = 3.6 Hz, 1H), 3.99-3.70 (m, 9H), 3.49-3.40 (m, 1H), 2.02 (s, 3H); $^{13}$C NMR (100 MHz, D$_2$O + 1 drop MeOH) $\delta$ 175.1, 97.7, 72.7, 71.5, 70.6, 68.9, 61.2, 54.3, 44.2, 22.5. LC-MS (ESI+) m/z calcd for C$_{10}$H$_{19}$ClNO$_6$ [M + H]$^+$ 284.1, found 284.1.

**Synthesis of compound 3:** $^{122, 125, 126}$ Compound 2 (4.0 g, 14.09 mmol, 1.0 equiv) was taken in DMF (8.0 mL) and NaN$_3$ (3.7 g, 56.39 mmol, 4.0 equiv) was added to the mixture and the reaction was heated at 85 °C for 5.0 h. At which point the $^1$H NMR spectrum of the reaction mixture indicated the complete consumption of the starting material. The heating was then turned off and the resulted suspension was filtered, and the filtrate was collected and concentrated to afford the crude product, which was purified by flash chromatography (DCM to 10% MeOH/DCM) to obtain a white solid (3.5 g, 86%) as the desired product. Compound 3 was synthesized in a one-pot reaction from the N-acetyl-D-glucosamine 1 in 74% yield following literature procedure.$^{122}$ ($R_f$ = 0.25 in 10% MeOH/DCM). M.p. 120.0-122.0 °C. $^1$H NMR (400 MHz, D$_2$O + 1 drop MeOH) $\delta$ 4.91 (d, $J$ = 3.6 Hz, 1H), 3.95-3.81 (m, 3H), 3.80-3.61 (m, 4H), 3.55-3.42 (m, 3H), 2.02 (s, 3H); $^{13}$C NMR (100 MHz, D$_2$O + 1 drop MeOH) $\delta$ 175.2, 97.6, 72.7, 71.5, 70.6, 67.2, 61.2, 54.2, 50.9, 22.5; LC-MS (ESI+) m/z calcd for C$_{10}$H$_{19}$N$_4$O$_6$ [M + H]$^+$ 291.1, found 291.1.

**Synthesis of compound 6a:** Compound 3 (200.0 mg, 0.69 mmol, 1 equiv) was added to a 50 mL round bottomed flask (RBF) with a drying tube and nitrogen balloon, pyridine (4.0 mL) was added and the reaction flask was cooled to 0 °C, then 4-bromobenzenesulfonyl chloride (352.1 mg, 1.37 mmol, 2.0 equiv) was added to the solution and the mixture was stirred at 0 °C and the ice bath was removed, the mixture was continuing stirred for about 20 h, at which time $^1$H NMR
spectrum showed about 95% conversion. The reaction was stopped, and solvent was removed, the crude product was purified on silica gel using a gradient of dichloromethane (DCM) and methanol, from pure DCM to up to 10% MeOH/DCM (R_f = 0.31 in 10% MeOH/DCM). The desired product was obtained as a colorless liquid (332.0 mg, 66%).^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 8.6 Hz, 2H), 6.21 (d, J = 8.8 Hz, 1H), 4.78 (d, J = 3.6 Hz, 1H), 4.38-4.29 (m, 2H), 4.11-4.04 (m, 1H), 3.87-3.78 (m, 2H), 3.71-3.65 (m, 1H), 3.60-3.54 (m, 1H), 3.53-3.46 (m, 2H), 3.37-3.29 (m, 1H), 2.02 (s, 3H); ^13C NMR (100 MHz, CDCl_3) δ 172.3, 134.8, 132.6, 129.5, 129.2, 97.7, 73.4, 70.5, 69.9, 69.7, 67.2, 53.2, 50.5, 23.2. HRMS m/z calcd for C_{16}H_{21}BrN_{4}O_{8}SNa [M + Na]⁺ 531.0156, found 531.0155.

**Synthesis of compound 6b:** Compound 3 (100.0 mg, 0.35 mmol, 1.0 equiv), pyridine (1.5 mL), 4-chlorobenzene sulfonyl chloride (147.7 mg, 0.69 mmol, 2.0 equiv), 12 h. Purified by flash chromatography (DCM to 2% MeOH/DCM) to obtain a colorless liquid (122.0 mg, 76%) as the desired compound. (R_f = 0.27 in 10% MeOH/DCM).^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 6.12 (d, J = 8.7 Hz, 1H), 4.79 (d, J = 3.6 Hz, 1H), 4.39-4.25 (m, 2H), 4.11-4.03 (m, 1H), 3.90-3.83 (m, 1H), 3.83-3.77 (m, 1H), 3.71-3.64 (m, 1H), 3.61-3.45 (m, 3H), 3.38-3.29 (m, 1H), 2.02 (s, 3H); ^13C NMR (100 MHz, CDCl_3) δ 172.3, 140.6, 134.3, 129.4, 97.7, 72.8, 70.3, 69.9, 69.8, 67.2, 53.2, 50.4, 23.1. LC-MS (ESI+) calcd for C_{16}H_{22}ClN_{4}O_{8}S [M+H]⁺ 465 found 465. HRMS (ESI+) ([M + Na]⁺) m/z calcd for C_{16}H_{21}ClN_{4}O_{8}SNa, 487.0661, found 487.0665.

**Synthesis of compound 6c:**^122 Compound 3 (160.0 mg, 0.55 mmol, 1.0 equiv), pyridine (1.5 mL), TsCl (210.2 mg, 1.10 mmol, 2.0 equiv), 10 h. Purified by flash chromatography (DCM to 10% MeOH/DCM) to obtain a white foam (186.0 mg, 76%) as the desired product. (R_f = 0.38 in 10% MeOH/DCM).^1H NMR (400 MHz, CDCl_3) δ 7.80 (d, J = 8.3 Hz, 2H), δ 7.34 (d, J = 8.3
Hz, 2H), 6.08 (d, J = 8.6 Hz, 1H), 4.81 (d, J = 3.8 Hz, 1H), 4.33 (dd, J = 11.0, 2.1 Hz, 1H), 4.26 (dd, J = 11.0, 5.7 Hz, 1H), 4.11-4.03 (m, 1H), 3.93-3.86 (m, 1H), 3.83-3.76 (m, 1H), 3.71-3.63 (t, J = 9.6 Hz, 1H), 3.62-3.43 (m, 3H), 3.35-3.28 (m, 1H), 2.57 (br s, 2H), 2.45 (s, 3H), 2.03 (s, 3H).

13C NMR (100 MHz, CDCl3) δ 172.4, 145.0, 132.8, 129.9, 128.0, 97.6, 73.7, 70.9, 69.9, 69.0, 67.3, 53.4, 50.5, 23.1, 21.7. LC-MS (ESI+) m/z calcd for C17H25N4O8S [M + H]+ 445, found 445.

Synthesis of compound 6d: Compound 3 (200.0 mg, 0.68 mmol, 1.0 equiv), pyridine (4.0 mL), 1-naphthalenesulfonyl chloride (312.4 mg, 1.37 mmol, 2.0 equiv), 20 h to see 90% conversion. Purified by flash chromatography (DCM to 10% MeOH/DCM) to obtain a white foam (211.0 mg, 64%) as the desired product. (Rf = 0.33 in 10% MeOH/DCM). 1H NMR (400 MHz, CDCl3) δ 8.63 (d, J = 7.9 Hz, 1 H), 8.29 (dd, J = 8.4, 7.0 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.74-7.55 (m, 3H), 5.92 (d, J = 8.3 Hz, 1H), 4.61 (d, J = 3.7 Hz, 1H), 4.40-4.31 (m, 1H), 4.28-4.20 (m, 1H), 3.98-3.89 (m, 1H), 3.90-3.67 (m, 2H), 3.64-3.54 (m, 1H), 3.49-3.34 (m, 3H), 3.27-3.18 (m, 1H), 2.01 (s, 3H); 13C NMR (400 MHz, CDCl3) δ 172.1, 135.3, 134.1, 131.1, 130.4, 128.8, 128.5, 128.4, 127.2, 125.0, 124.0, 97.4, 72.7, 70.4, 69.9, 69.8, 66.9, 53.1, 50.3, 23.1. HRMS m/z calcd for C20H24N4O8SNa [M + Na]+ 503.1207, found 503.1208.

Synthesis of compound 7a: Compound 6a (100.0 mg, 0.2 mmol, 1.0 equiv) was added to a 50 mL round bottom flask with a drying tube and nitrogen balloon attached, the reaction flask was cooled to 0 ºC, then dichloromethane (2.5 mL), pyridine (5.0 equiv) and benzoyl chloride (0.06 mL, 0.5 mmol, 2.5 equiv) were added to the solution. The reaction mixture was stirred at to 0 ºC and then stirred at rt for about 12 h. At this time, TLC and 1H NMR indicated full conversion to the product. The reaction was stopped, and solvent was removed under vacuum using a rotavap. The crude product was purified using flash chromatography on silica gel using a solvent gradient of ethyl acetate and hexane from 1:4 to 3:2 ratio. The desired product was obtained as a colorless
viscous liquid (112.0 mg, 79% yield). (Rf = 0.38 in 5% MeOH/DCM). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.90-7.83 (m, 4H), 7.70 (d, \(J = 8.5\) Hz, 2H), 7.58 (d, \(J = 8.5\) Hz, 2H), 7.55-7.47 (m, 2H), 7.39-7.32 (m, 4H), 5.90 (d, \(J = 9.1\) Hz, 1H), 5.64 (t, \(J = 10.9\) Hz, 1H), 5.38 (t, \(J = 9.9\) Hz, 1H), 4.97 (d, \(J = 3.6\) Hz, 1H), 4.56-4.49 (m, 1H), 4.28-4.16 (m, 3H), 4.00-3.94 (m, 1H), 3.72-3.65 (m, 1H), 3.62-3.55 (m, 1H), 3.45-3.38 (m, 1H), 1.85 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 170.1, 166.9, 165.1, 134.5, 133.7, 133.5, 132.5, 129.9, 129.8, 129.4, 129.3, 128.7, 128.5, 128.4, 97.6, 71.0, 68.8, 68.5, 68.4, 67.8, 52.0, 50.4, 23.0. HRMS m/z calcd for C\(_{30}\)H\(_{29}\)BrN\(_4\)O\(_{10}\)Na [M + Na\(^+\)] 739.0680, found 739.0676.

**Synthesis of compound 7b:** Compound 6b (100.0 mg, 0.22 mmol, 1.0 equiv), DCM (3.0 mL) and benzoyl chloride (0.06 mL, 0.54 mmol, 2.5 equiv), 12 h. The crude was purified using flash chromatography on silica gel using a solvent gradient of DCM to 3% MeOH/DCM) to obtain brown oil (96.0 mg, 66%) as the desired product. (Rf = 0.32 in 5% MeOH/DCM). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.96-7.87 (m, 4H), 7.53-7.45 (m, 2H), 7.40-7.30 (m, 4H), 5.96 (d, \(J = 9.3\) Hz, 1H), 5.68 (t, \(J = 9.9\) Hz, 1H), 5.06 (d, \(J = 3.6\) Hz, 1H), 4.65-4.55 (m, 1H), 4.26-4.18 (m, 1H), 4.12-4.03 (m, 1H), 3.78-3.71 (m, 1H), 3.71-3.63 (m, 2H), 3.63-3.56 (m, 1H), 3.48-3.39 (m, 1H), 1.86 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 170.1, 167.0, 165.2, 133.6, 133.5, 129.83, 129.81, 128.7, 128.6, 128.5, 128.4, 97.5, 71.2, 70.5, 70.3, 67.7, 52.1, 50.4, 43.6, 23.0. LC-HRMS m/z calcd for C\(_{24}\)H\(_{25}\)ClN\(_4\)O\(_7\)Na [M + Na\(^+\)] 539.1304, found 539.1301.

**Synthesis of compound 7c:**\(^{122}\) To a 50 mL round bottom flask, compound 6c (500.0 mg, 1.12 mmol, 1.0 equiv), DCM (5.0 mL), pyridine (0.45 mL, 5.62 mmol, 5.0 equiv) were added in the given order and the mixture was cooled to 0 °C. To the stirring mixture benzoyl chloride (0.32 mL, 2.81 mmol, 2.5 equiv) was added dropwise. The mixture was allowed to warm up to room temperature and the stirring was continued for 4 more h. \(^1\)H NMR spectrum indicated the
completion of the reaction. Work up was performed with H$_2$O (25 mL) and DCM (25 mL x 3). The combined organic layer was dried over Na$_2$SO$_4$ (anhydrous), filtered and concentrated to afford the crude, which was purified by column chromatography using eluent from pure DCM to 2% MeOH/DCM to give a colorless oil (572 mg, 72%) as the desired product ($R_f$ = 0.6 in 5% MeOH/DCM). Compound 7c was also synthesized in a one-pot reaction from compound 3 following the literature procedure.$^{122}$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.91-7.83 (m, 4H), 7.71 (d, $J$ = 8.3 Hz, 2H), 7.55-7.45 (m, 2H), 7.39-7.31 (m, 4H), 7.22 (d, $J$ = 8.1 Hz, 2H), 5.91 (d, $J$ = 9.5 Hz, 1H), 5.62 (dd, $J$ = 10.9, 9.5 Hz, 1H), 5.36 (t, $J$ = 9.5 Hz, 1H), 4.96 (d, $J$ = 3.6 Hz, 1H), 4.56-4.48 (m, 1H), 4.29-4.10 (m, 3H), 4.03-3.97 (m, 1H), 3.71-3.64 (m, 1H), 3.63-3.55 (m, 1H), 3.44-3.36 (m, 1H), 2.37 (s, 3H), 1.85 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.1, 166.9, 165.1, 145.0, 133.6, 133.5, 132.4, 130.0, 129.84, 129.78, 128.7, 128.6, 128.4, 128.3, 128.0, 97.5, 71.1, 68.9, 68.6, 68.3, 67.8, 52.0, 50.4, 23.0, 21.6; LC-MS (ESI+) m/z calcd for C$_{31}$H$_{33}$N$_4$O$_{10}$S $[M + H]^+$ 653.2, found 653.2.

**Synthesis of compound 8a:** To a 50 mL RBF, 7a (100.0 mg, 0.14 mmol, 1.0 equiv) in t-BuOH: THF: H$_2$O (v:v:v 1:1:1, 3.0 mL) and 10-undecynoic acid (33.1 mg, 0.18 mmol, 1.3 equiv), CuSO$_4$·5H$_2$O (7.0 mg, 0.028 mmol, 0.2 equiv) and sodium ascorbate (NaAsc) (11.1 mg, 0.056 mmol, 0.4 equiv) was added sequentially as described and stirred at rt for 16 h. The reaction was monitored after 16 h by $^1$H NMR to see the consumption of starting material and TLC to see no starting material at all. Further purified by flash chromatography using pure DCM to 2% MeOH/DCM to obtain a white foam (112.0 mg, 88%) as the desired product. ($R_f$ = 0.26 in 5% MeOH/DCM). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.88-7.79 (m, 4H), 7.68 (d, $J$ = 8.6 Hz, 2H), 7.56 (d, $J$ = 8.6 Hz, 2H), 7.53-7.44 (m, 3H), 7.38-7.30 (m, 4H), 6.15 (d, $J$ = 9.0 Hz, 1H), 5.52 (t, $J$ = 10.1 Hz, 1H), 5.32 (t, $J$ = 9.8 Hz, 1H), 4.87 (d, $J$ = 3.6 Hz, 1H), 4.60 (s, 2H), 4.53-4.44 (m, 1H),
4.20-4.06 (m, 3H), 4.02-3.94 (m, 1H), 3.92-3.84 (m, 1H), 2.70 (s, 2H), 2.30 (t, J = 7.3 Hz, 2H), 1.86 (s, 3H), 1.68-1.54 (m, 4H), 1.26 (s, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 177.7, 170.6, 166.8, 165.0, 134.3, 133.6, 133.4, 132.5, 129.8, 129.7, 129.4, 129.2, 128.6, 128.5, 128.40, 128.37, 97.5, 71.1, 68.7, 68.4, 68.3, 66.6, 51.8, 49.6, 33.9, 29.2, 29.0, 28.91, 28.86, 25.5, 24.7, 22.9. HRMS m/z calcd for C$_{41}$H$_{47}$BrN$_4$O$_4$SNa [M + Na]$^+$ 921.1990, found 921.1994.

**Synthesis of compound 8b:** Compound 7b (90.0 mg, 0.13 mmol, 1.0 equiv), t-BuOH: THF: H$_2$O (v:v:v 1:1:1, 2.5 mL), 10-undecynoic acid (31.7 mg, 0.17 mmol, 1.3 equiv), CuSO$_4$·5H$_2$O (6.7 mg, 0.02 mmol, 0.2 equiv), NaAsc (10.6 mg, 0.05 mmol, 0.4 equiv), 5 h. The crude was purified by flash chromatography (DCM to 3% MeOH/DCM) to obtain a colorless oil (68 mg, 60%) as the desired product. ($R_f = 0.24$ in 5% MeOH/DCM). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.94-7.86 (m, 4H), 7.54-7.46 (m, 2H), 7.44 (s, 1H), 7.40-7.32 (m, 4H), 6.13 (d, J = 9.2 Hz, 1H), 5.58 (dd, J = 10.7, 9.6 Hz, 1H), 5.41 (t, J = 9.6 Hz, 1H), 4.96 (d, J = 3.6 Hz, 1H), 4.70-4.59 (m, 2H), 4.59-4.51 (m, 1H), 4.31-4.20 (m, 1H), 4.03-3.89 (m, 2H), 3.68-3.57 (m, 2H), 2.73 (t, J = 7.6 Hz, 2H), 2.33 (t, J = 7.3 Hz, 2H), 1.88 (s, 3H), 1.69-1.58 (m, 4H), 1.29 (s, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.6, 167.0, 165.2, 133.6, 133.5, 129.9, 129.8, 128.73, 128.65, 128.5, 128.4, 97.5, 71.4, 70.5, 70.3, 66.6, 52.0, 49.5, 43.6, 29.2, 28.9, 28.8, 28.7, 25.6, 23.0. HRMS m/z calcd for C$_{35}$H$_{45}$ClN$_4$O$_9$Na [M + Na]$^+$ 721.2611, found 721.2609.

**Synthesis of compound 8c:** Compound 7c (360.0 mg, 0.55 mmol, 1 equiv), t-BuOH: THF: H$_2$O (v:v:v 1:1:1, 6.0 mL), 10-undecynoic acid (138.0 mg, 0.72 mmol, 1.3 equiv), CuSO$_4$·5H$_2$O (18.0 mg, 0.108 mmol, 0.2 equiv), NaAsc (44.0 mg, 0.22 mmol, 0.4 equiv), 12 h. Purified by flash chromatography (DCM to 5% MeOH/DCM) to afford the colorless a semi-solid (378.0 mg, 83%) as the desired product ($R_f = 0.65$ in 10% MeOH/DCM). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.89-7.81 (m, 4H), 7.70 (d, J = 8.3 Hz, 2H), 7.55-7.43 (m, 3H), 7.40-7.30 (m, 4H), 7.21 (d, J = 8.1 Hz, 2H),
6.07 (d, J = 9.2 Hz, 1H), 5.54 (dd, J = 10.8, 9.6 Hz, 1H), 5.30 (t, J = 9.6 Hz, 1H), 4.86 (d, J = 3.6 Hz, 1H), 4.65-4.56 (m, 2H), 4.51-4.43 (m, 1H), 4.22-4.04 (m, 4H), 3.93-3.85 (m, 1H), 2.72 (t, J = 7.7 Hz, 2H), 2.36 (s, 3H), 2.32 (t, J = 7.4 Hz, 2H), 1.86 (s, 3H), 1.71-1.57 (m, 4H), 1.29 (br s, 8H); 
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 177.0, 170.5, 166.9, 165.1, 148.8, 145.0, 133.6, 133.4, 132.3, 130.0, 129.9, 129.81, 129.78, 128.7, 128.6, 128.4, 128.0, 121.3, 97.5, 71.3, 68.9, 68.7, 68.2, 66.7, 51.9, 49.5, 33.8, 29.3, 29.0, 28.84, 28.82, 25.6, 24.7, 23.0, 21.6; HRMS m/z calcd for C\(_{42}\)H\(_{50}\)N\(_4\)O\(_{21}\)SNa [M + Na]"^+" 857.3038, found 857.3039.

**Synthesis of compound 4:**\(^{127}\) N-acetyl-D-glucosamine 1 (5.0 g, 22.6 mmol, 1.0 equiv) was added to a 100 mL round bottomed flask (RBF) with 3-chloro-1-propanol (7.56 mL, 90.4 mmol, 4.0 equiv) and BF\(_3\)•Et\(_2\)O (0.56 mL, 4.5 mmol, 0.2 equiv). The reaction mixture was stirred at 85 °C for 6.0 h. The heating was turned off and the mixture was cooled room temperature. The mixture was then treated with water (15 mL) and washed with DCM (20 mL x 2) to remove excess 3-chloro-1-propanol. The aqueous layer was then collected and evaporated. The crude product was obtained as a dark brown oily crude. It was then dissolved in MeOH and coated on to SiO\(_2\) (dry loading) for purification. The crude was then purified by chromatography on silica gel using a gradient of dichloromethane (DCM) and methanol from pure DCM to up to 10% MeOH/DCM. The desired product was obtained as a white solid (4.63 g, 69%); R\(_f\) = 0.16 in 10% MeOH/DCM; m.p. 146.0-148.0 °C. \(^1\)H NMR (400 MHz, D\(_2\)O) \(\delta\) 4.85 (d, J =3.6 Hz, 1H), 3.91-3.81 (m, 3H), 3.78-3.66 (m, 5H), 3.59-3.53 (m, 1H), 3.50-3.42 (m, 1H), 2.08-1.99 (m, 5H); \(^{13}\)C NMR (100 MHz, D\(_2\)O) \(\delta\) 174.5, 97.0, 71.9, 71.0, 70.0, 64.6, 60.6, 53.8, 42.1, 31.4, 21.9. LC-MS (ESI+) m/z calcd for C\(_{11}\)H\(_{21}\)ClNO\(_6\) [M + H]^+ 298.2, found 298.1.

**Synthesis of compound 5:**\(^{122,127}\) To a solution of compound 4 (5.0 g, 16.79 mmol, 1.0 equiv) in DMF (10.0 mL) was added NaN\(_3\) (3.3 g, 50.38 mmol, 3.0 equiv) and the mixture was
heated at 85 °C for 5.0 h. At which point the $^1$H NMR spectrum of the reaction mixture indicated the complete consumption of the starting material. DMF was removed under reduced pressure to obtain the crude which was further purified by flash chromatography (DCM to 7% MeOH/DCM) to obtain a white solid (4.2 g, 82%) as the desired product (R$_f$ = 0.25 in 10% MeOH/DCM).

Compound 5 was also synthesized in a one-pot reaction from the $N$-acetyl-D-glucosamine 1 following the literature.$^{122}$ m.p. 125.0-127.0 °C. $^1$H NMR (400 MHz, D$_2$O) $\delta$ 4.84 (d, $J$ = 3.6 Hz, 1H), 3.91-3.63 (m, 6H), 3.54-3.40 (m, 4H), 2.01 (s, 3H), 1.91-1.83 (m, 2H); $^{13}$C NMR (100 MHz, D$_2$O) $\delta$ 175.0, 97.5, 72.5, 71.6, 70.6, 65.6, 61.2, 54.4, 48.8, 28.6, 22.5; LC-MS (ESI+) m/z calcd for C$_{11}$H$_{21}$N$_4$O$_6$ [M + H]$^+$ 305.1, found 305.1.

**Synthesis of compound 6e:** $^{122}$ To a stirring solution of compound 5 (1.50 g, 4.91 mmol, 1 equiv) in dry pyridine (7 mL) at 0 °C, a solution of TsCl (1.88 g, 9.82 mmol, 2 equiv) in pyridine (2 mL) was added dropwise and the mixture was left stirring at room temperature for 12 h. The reaction was quenched with MeOH (2.0 mL) and the solvent was evaporated. The crude product was purified by chromatography on SiO$_2$ using eluent from 1% MeOH/DCM to 5% MeOH/DCM to obtain an off-white foam (1.47 g, 65%) as the desired product (R$_f$ = 0.32 in 5% MeOH/DCM).

$^1$H NMR (400 MHz, CDCl$_3$) 7.81 (d, $J$ = 8.3 Hz, 2H), 7.36 (d, $J$ = 8.2 Hz, 2H), 6.49 (d, $J$ = 8.8 Hz, 1H), 4.73 (d, $J$ = 3.5 Hz, 1 H), 4.35-4.29 (m, 2H), 4.02 (dt, $J$ = 19.4, 3.4 Hz, 1H), 3.85-3.67 (m, 5H), 3.53-3.34 (m, 4H), 2.45 (s, 3H), 2.04 (s, 3H), 1.86 (pentet, $J$ = 6.2 Hz, 2H); $^{13}$C NMR (400 MHz, CDCl$_3$) 172.1, 145.0, 132.8, 129.9, 128.0, 97.4, 73.1, 70.4, 69.8, 69.4, 65.1, 53.4, 48.6, 28.5, 23.1, 21.6. LC-MS (ESI+) m/z calcd for C$_{18}$H$_{27}$N$_4$O$_8$S [M + H]$^+$ 459, found 459.

**Synthesis of compound 9:** $^{122}$ To a 50 mL round bottom flask, compound 6e (1.0 g, 2.18 mmol, 1.0 equiv), DCM (8.0 mL), pyridine (0.88 mL, 10.90 mmol, 5.0 equiv) were added in the given order and the mixture was cooled to 0 °C. To the stirring mixture benzyol chloride (0.63
mL, 5.45 mmol, 2.5 equiv) was added dropwise. The mixture was left stirring at room temperature for 8 more h. \(^1\)H NMR spectrum indicated the completion of the reaction. Work up was performed with H\(_2\)O (40 mL) and DCM (50 mL x 3). The combined organic layer was dried over Na\(_2\)SO\(_4\) (anhydrous), filtered and concentrated to afford the crude, which was purified by column chromatography using eluent from DCM to 2% MeOH/DCM to give a colorless oil (1.13 g, 78%) as the desired product (R\(_f\) = 0.65 in 5% MeOH/DCM). Compound 9 was also synthesized using a one-pot reaction from compound 5 directly following the literature procedure. \(^{122}\) \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.90-7.83 (m, 4H), 7.71 (d, \(J = 8.3\) Hz, 2H), 7.55-7.48 (m, 2H), 7.40-7.31 (m, 4H), 7.22 (d, \(J = 8.1\) Hz, 2H), 5.89 (d, \(J = 9.2\) Hz, 1H), 5.59 (dd, \(J = 10.9, 9.5\) Hz, 1H), 5.35 (t, \(J = 9.5\) Hz, 1H), 4.90 (d, \(J = 3.6\) Hz, 1H), 4.48 (ddd, \(J = 10.9, 9.2, 3.6\) Hz, 1H), 4.25-4.10 (m, 3H), 3.87 (dt, \(J = 10.1, 6.0\) Hz, 1H), 3.59-3.41 (m, 3H), 2.37 (s, 3H), 2.00-1.92 (m, 2H), 1.85 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 169.9, 167.1, 165.1, 145.0, 133.53, 133.49, 132.5, 129.84, 129.78, 129.76, 128.7, 128.6, 128.43, 128.42, 128.0, 97.3, 71.4, 68.9, 68.4, 68.2, 65.6, 52.2, 48.6, 28.6, 23.1, 21.6. LC-MS (ESI+) m/z C\(_{32}\)H\(_{35}\)N\(_4\)O\(_{10}\)S [M + H]\(^+\) 667.2, found 667.2.

**Synthesis of compound LM28, 13c:** The intermediate 8c (100.0 mg, 0.12 mmol, 1 equiv), K\(_2\)CO\(_3\) (33.0 mg, 0.24 mmol, 2.0 equiv) and DMF (14 mL) were added to a 50 mL RBF. The reaction mixture was stirred at 70 °C for 3 h, at which time \(^1\)H NMR spectrum and TLC indicated the full conversion of starting materials. The reaction was stopped, and solvent was removed under reduced pressure to afford the crude product. The crude was purified via flash chromatography using an eluent of pure DCM to 5% MeOH/DCM to obtain the desired product as a white solid (65.0 mg, 82%), R\(_f\) = 0.29 in 5% MeOH/DCM), m.p. 196.0 °C to 198.0 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.95-7.86 (m, 4H), 7.54-7.45 (m, 2H), 7.42 (s, 1H), 7.40-7.31 (m, 4H), 6.00 (d, \(J = 9.2\) Hz, 1H), 5.62 (dd, \(J = 10.9, 9.7\) Hz, 1H), 5.45 (t, \(J = 9.7\) Hz, 1H), 4.77-4.69 (m, 1H), 4.66 (d,
$J = 3.5 \text{ Hz, 1H}$, 4.62-4.54 (m, 1H), 4.51-4.43 (m, 1H), 4.41-4.34 (m, 1H), 4.13-4.01 (m, 4H), 2.87-2.78 (m, 1H), 2.77-2.67 (m, 1H), 2.31-2.20 (m, 1H), 2.19-2.09 (m, 1H), 1.93 (s, 3H), 1.79-1.60 (m, 2H), 1.56-1.43 (m, 2H), 1.29-1.09 (m, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.4, 170.2, 167.2, 165.4, 133.52, 133.47, 129.9, 129.8, 128.9, 128.8, 128.5, 128.4, 121.3, 97.7, 71.4, 70.2, 68.0, 65.0, 63.2, 52.6, 46.6, 33.7, 30.2, 28.20, 28.19, 28.1, 27.7, 27.2, 24.9, 24.4, 23.1; HRMS (ESI+) ([M + Na]$^+$) m/z calcd for C$_{35}$H$_{42}$N$_4$O$_9$Na, 685.2844, found 685.2825.

**Synthesis of compound LM28 and DLM28:** Compound 8a (100.0 mg, 0.11 mmol, 1.0 equiv), DMF (7.0 mL), and K$_2$CO$_3$ (30.7 mg, 0.22 mmol, 2.0 equiv) were added to a 50 mL RBF. The reaction mixture was stirred at 75 °C for 5 h, the $^1$H NMR and TLC samples showed complete conversion of the starting materials. The crude was purified by flash chromatography using pure DCM to 5% MeOH DCM to obtain the desired compound LM28 (53.0 mg, 0.080 mmol, 73%) along with some later fraction which was identified as the dimerization product DLM28 as a white solid (15.0 mg, 0.011 mmol, 20% based on starting material conversion). The chloro compound 8b was cyclized by similar conditions, using compound 8b (50.0 mg, 0.07 mmol, 1.0 equiv), DMF (7.0 mL), and K$_2$CO$_3$ (19.8 mg, 0.14 mmol, 2.0 equiv). The desired compound LM28 (31.7 mg, 0.048 mmol, 68%) and DLM28 (8.0 mg, 0.006 mmol, 17% based on starting material conversion) were obtained. Characterization for the dimerized compound: R$_f$ = 0.18 in 5% MeOH/DCM. M.p. 236.0-238.0 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.92-7.87 (m, 4H), 7.51-7.46 (m, 3H), 7.37-7.31 (m, 4H), 6.06 (d, $J = 9.1$ Hz, 1H), 5.58 (dd, $J = 10.3, 9.5$ Hz, 1H), 5.43 (t, $J = 9.8$ Hz, 1H), 4.89 (d, $J = 3.5$ Hz, 1H), 4.63-4.50 (m, 3H), 4.21-4.11 (m, 3H), 3.95-3.88 (m, 2H), 2.72 (t, $J = 7.6$ Hz, 2H), 2.27-2.22 (m, 2H), 1.89 (s, 3H), 1.70-1.66 (m, 2H), 1.59-1.54 (m, 2H), 1.33-1.23 (m, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.2, 170.3, 166.9, 165.2, 133.5, 133.4, 129.83, 129.77, 128.87,
3-azido propionic acid (200.0 mg, 1.7 mmol, 1.0 equiv) and 1,7-octadiyne (276.0 mg, 2.6 mmol, 1.5 equiv) were dissolved in t-BuOH: THF: H2O (v:v:v 1:1:1, 25.0 mL), then CuSO4·5H2O (84.8 mg, 0.34 mmol, 0.2 equiv), NaAsc (134.7 mg, 0.68 mmol, 0.4 equiv) were added to the reaction mixture. The reaction was stirred rt for 24 h to at which time the starting material was full converted to product, as indicated by 1H NMR and TLC. The reaction was stopped, and solvent was removed using a rotavap, the residue was diluted with EtOAc and acidified using 0.1 N HCl (5.0 mL) followed by water wash. The organic layer was collected and dried over anhydrous Na2SO4 and solvent was removed under vacuum to obtain the crude, which was further purified with flash chromatography using eluent of hexanes to 60% EtOAc/Hexanes to obtain the desired product as a yellowish solid (272.0 mg, 70%), Rf = 0.48 in 80% EtOAc/Hexanes, m.p. 93.5-94.5 °C; 1H NMR (400 MHz, CDCl3) δ 8.98 (br s, 1H), 7.47 (s, 1H), 4.66 (t, J = 6.5 Hz, 2H), 3.02 (t, J = 6.5 Hz, 2H), 2.75 (t, J = 7.6 Hz, 2H), 2.23-2.18 (m, 2H), 1.92 (t, J = 2.6 Hz, 1H), 1.82-1.73 (m, 2H), 1.62-1.54 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 173.2, 147.7, 121.8, 84.2, 68.5, 45.7, 34.7, 28.3, 27.9, 24.9, 18.1. HRMS m/z calcd for C11H15N3O2Na [M + Na]+ 244.1056, found 244.1056.

Synthesis of compound 10e: The same procedure for compound 10d was used, 3-azido propionic acid (200.0 mg, 1.7 mmol, 1.0 equiv), t-BuOH: THF: H2O (v:v:v 1:1:1, 25.0 mL), 1,8-nonadiyne (313.3 mg, 2.6 mmol, 1.5 equiv), CuSO4·5H2O (84.8 mg, 0.34 mmol, 0.2 equiv), NaAsc (134.7 mg, 0.68 mmol, 0.4 equiv), 24 h. The product was purified using flash chromatography (Hexanes to 30% EtOAc/Hexanes) to obtain a yellowish solid (306.0 mg, 75%) as the desired product (Rf = 0.5 in 80% EtOAc/Hexanes). M.p. 137.5-139.0 °C; 1H NMR (400 MHz, CDCl3)
7.39 (s, 1H), 4.62 (t, $J = 6.5$ Hz, 2H), 3.02 (t, $J = 6.5$ Hz, 2H), 2.71 (t, $J = 7.7$ Hz, 2H), 2.23-2.13 (m, 2H), 1.93 (t, $J = 2.7$ Hz, 1H), 1.72-1.64 (m, 2H), 1.59-1.51 (m, 2H), 1.50-1.43 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.0, 148.0, 121.6, 84.5, 68.3, 45.5, 34.6, 28.8, 28.3, 28.2, 25.4, 18.3. HRMS (ESI+) m/z calcld for C$_{12}$H$_{17}$N$_3$O$_2$Na $[M + Na]^+$ 258.1213, found 258.1212.

Synthesis of compound 11a: Compound 7c (100.0 mg, 0.15 mmol, 1.0 equiv), t-BuOH: THF: H$_2$O (v:v:v 1:1:1, 3.0 mL), 6-heptynoic acid (25.2 mg, 0.2 mmol, 1.3 equiv), CuSO$_4$·5H$_2$O (7.7 mg, 0.03 mmol, 0.2 equiv), NaAsc (12.1 mg, 0.06 mmol, 0.4 equiv), 16 h. Purified by flash chromatography (DCM to 3% MeOH/DCM) to obtain a colorless slurry (96.0 mg, 81%) as the desired product ($R_f = 0.32$ in 5% MeOH/DCM). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.88-7.83 (m, 4H), 7.70 (d, $J = 8.2$ Hz, 2H), 7.67 (s, 1H), 7.55-7.47 (m, 3H), 7.40-7.32 (m, 5H), 7.22 (d, $J = 8.0$ Hz, 2H), 6.45 (d, $J = 8.8$ Hz, 1H), 5.62 (t, $J = 10.1$ Hz, 1H), 5.31 (t, $J = 9.4$ Hz, 1H), 4.90 (d, $J = 3.6$ Hz, 1H), 4.70-4.59 (m, 2H), 4.57-4.49 (m, 1H), 4.22-4.07 (m, 4H), 3.97-3.90 (m, 1H), 2.85-2.77 (m, 2H), 2.43-2.34 (m, 5H), 1.85 (s, 3H), 1.81-1.68 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 176.5, 170.6, 167.5, 165.1, 145.1, 133.8, 133.6, 132.3, 129.9, 129.8, 128.53, 128.46, 128.0, 97.2, 71.6, 69.1, 68.5, 68.3, 66.4, 51.8, 32.8, 27.8, 24.9, 23.5, 22.9, 21.6. HRMS m/z calcld for C$_{38}$H$_{42}$N$_4$O$_{12}$SNa $[M + Na]^+$ 801.2412, found 801.2406.

Synthesis of compound 11b: Compound 7c (100.0 mg, 0.15 mmol, 1.0 equiv), t-BuOH: THF: H$_2$O (v:v:v 1:1:1, 3.0 mL), 8-nonynoic acid (30.7 mg, 0.2 mmol, 1.3 equiv), CuSO$_4$·5H$_2$O (7.7 mg, 0.03 mmol, 0.2 equiv), NaAsc (12.1 mg, 0.06 mmol, 0.4 equiv), 16 h. Purified by flash chromatography (DCM to 3% MeOH/DCM) to obtain a colorless slurry (109.0 mg, 87%) as the desired product ($R_f = 0.38$ in 5% MeOH/DCM). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.88-7.82 (m, 4H), 7.70 (d, $J = 8.0$ Hz, 2H), 7.54-7.45 (m, 3H), 7.38-7.30 (m, 4H), 7.21 (d, $J = 7.9$ Hz, 2H), 6.15 (d, $J = 6.9$ Hz, 1H), 5.55 (t, $J = 10.1$ Hz, 1H), 5.29 (t, $J = 8.6$ Hz, 1H), 4.86 (d, $J = 2.4$ Hz, 1H), 4.60
(br s, 2H), 4.52-4.43 (m, 1H), 4.20-4.05 (m, 4H), 3.90-3.84 (m, 1H), 2.73 (br s, 2H), 2.35 (s, 3H), 2.31 (t, J = 7.2 Hz, 2H), 1.86 (s, 3H), 1.72-1.58 (m, 4H), 1.38-1.33 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 176.6, 169.6, 165.9, 164.1, 144.1, 132.6, 132.5, 131.3, 128.9, 128.8, 127.7, 127.6, 127.4, 127.0, 96.5, 70.3, 67.9, 67.6, 67.3, 65.5, 50.8, 32.7, 27.47, 27.45, 23.5, 20.6. HRMS m/z calcd for C$_{40}$H$_{46}$N$_4$O$_{12}$SNa [M + Na]$^+$ 829.2725, found 829.2722.

**Synthesis of compound 12a:** Compound 9 (100.0 mg, 0.15 mmol, 1.0 equiv), t-BuOH: THF: H$_2$O (v:v:v 1:1:1, 2.5 mL), 6-heptynoic acid (24.6 mg, 0.19 mmol, 1.3 equiv), CuSO$_4$·5H$_2$O (7.5 mg, 0.03 mmol, 0.2 equiv), NaAsc (11.8 mg, 0.06 mmol, 0.4 equiv), 24 h. Purified by flash chromatography (DCM to 2% MeOH/DCM) to obtain a colorless slurry (98.0 mg, 82%) as the desired product (R$_f$ = 0.22 in 5% MeOH/DCM). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.92-7.83 (m, 4H), 7.69 (d, J = 8.3 Hz, 2H), 7.56-7.46 (m, 3H), 7.40-7.32 (m, 4H), 7.21 (d, J = 8.2 Hz, 2H), 6.43 (d, J = 9.2 Hz, 1H), 5.61 (t, J = 10.1 Hz, 1H), 5.32 (t, J = 10.0 Hz, 1H), 4.88 (d, J = 3.6 Hz, 1H), 4.66-4.57 (m, 1H), 4.54-4.42 (m, 2H), 4.31-4.23 (m, 1H), 4.21-4.08 (m, 2H), 3.82-3.74 (m, 1H), 3.43-3.33 (m, 1H), 2.79 (t, J = 6.7 Hz, 2H), 2.42-2.33 (m, 5H), 2.29-2.19 (m, 2H), 1.93 (s, 3H), 1.81-1.64 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 176.4, 170.9, 167.1, 165.2, 148.1, 145.0, 133.6, 132.3, 129.9, 129.8, 128.7, 128.6, 128.5, 128.4, 128.0, 121.3, 97.1, 71.5, 69.1, 68.5, 68.4, 64.5, 52.1, 46.8, 33.1, 29.6, 28.2, 25.0, 23.8, 23.0, 21.6. HRMS m/z calcd for C$_{39}$H$_{44}$N$_4$O$_{12}$SNa [M + Na]$^+$ 815.2569, found 815.2564.

**Synthesis of compound 12b:** Compound 9 (100.0 mg, 0.15 mmol, 1.0 equiv), t-BuOH: THF: H$_2$O (v:v:v 1:1:1, 2.5 mL), 8-nonynoic acid (30.1 mg, 0.19 mmol, 1.3 equiv), CuSO$_4$·5H$_2$O (7.5 mg, 0.03 mmol, 0.2 equiv), NaAsc (11.8 mg, 0.06 mmol, 0.4 equiv), 24 h. Purified by flash chromatography (DCM to 2% MeOH/DCM) to obtain a colorless slurry (106.0 mg, 86%) as the desired product (R$_f$ = 0.23 in 5% MeOH/DCM). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.92-7.84 (m, 4H),
7.69 (d, $J = 8.2$ Hz, 2H), 7.56-7.46 (m, 2H), 7.41-7.31 (m, 5H), 7.21 (d, $J = 8.2$ Hz, 2H), 6.38 (d, $J = 9.2$ Hz, 1H), 5.60 (t, $J = 10.0$ Hz, 1H), 5.31 (t, $J = 9.9$ Hz, 1H), 4.84 (d, $J = 3.5$ Hz, 1H), 4.67-4.57 (m, 1H), 4.55-4.43 (m, 2H), 4.31-4.24 (m, 1H), 4.20-4.07 (m, 2H), 3.87-3.78 (m, 1H), 3.40-3.31 (m, 1H), 2.74 (t, $J = 7.5$ Hz, 2H), 2.38-2.18 (m, 7H), 1.95 (s, 3H), 1.74-1.65 (m, 4H), 1.42-1.32 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 176.9, 170.8, 167.0, 165.2, 148.5, 145.0, 133.5, 133.4, 132.3, 129.9, 129.8, 128.8, 128.4, 128.0, 120.9, 97.5, 71.5, 69.2, 68.6, 68.5, 64.8, 52.0, 46.9, 33.5, 29.9, 28.9, 28.44, 28.37, 25.2, 24.5, 23.0, 21.6. HRMS m/z calcd for C$_{41}$H$_{48}$N$_4$O$_{12}$SNa $[M + Na]^+$ 843.2882, found 843.2876.

**Synthesis of compound 12c:** Compound 9 (100.0 mg, 0.15 mmol, 1.0 equiv), $t$-BuOH: THF: H$_2$O (v:v:v 1:1:1, 2.5 mL), 10-undecynoic acid (35.5 mg, 0.19 mmol, 1.3 equiv), CuSO$_4$·5H$_2$O (7.5 mg, 0.03 mmol, 0.2 equiv), NaAsc (11.8 mg, 0.06 mmol, 0.4 equiv), 24 h. Purified by flash chromatography using (DCM to 2% MeOH/DCM) to obtain a colorless slurry (98.0 mg, 77%) as the desired product ($R_f = 0.27$ in 5% MeOH/DCM). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.91-7.84 (m, 4H), 7.69 (d, $J = 8.2$ Hz, 2H), 7.55-7.44 (m, 2H), 7.41-7.30 (m, 5H), 7.20 (d, $J = 8.2$ Hz, 2H), 6.44 (d, $J = 9.2$ Hz, 1H), 5.59 (t, $J = 10.1$ Hz, 1H), 5.31 (t, $J = 9.8$ Hz, 1H), 4.83 (d, $J = 3.5$ Hz, 1H), 4.70-4.57 (m, 1H), 4.56-4.43 (m, 2H), 4.32-4.23 (m, 1H), 4.20-4.06 (m, 2H), 3.89-3.80 (m, 1H), 3.40-3.28 (m, 1H), 2.72 (t, $J = 7.6$ Hz, 2H), 2.37-2.17 (m, 7H), 1.94 (s, 3H), 1.71-1.55 (m, 4H), 1.39-1.24 (m, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 177.8, 170.8, 166.9, 165.2, 148.9, 145.0, 133.5, 133.4, 132.3, 129.84, 129.79, 129.77, 128.8, 128.6, 128.4, 128.1, 128.0, 120.7, 97.5, 71.4, 69.2, 68.5, 68.4, 64.8, 51.9, 46.8, 33.9, 29.9, 29.2, 28.92, 28.89, 28.85, 25.5, 24.6, 23.0, 21.6. HRMS m/z calcd for C$_{43}$H$_{52}$N$_4$O$_{12}$SNa $[M + Na]^+$ 871.3195, found 871.3192.

**Synthesis of compound 13a (LM24):** Compound 11a (74.0 mg, 0.095 mmol, 1.0 equiv), DMF (13.0 mL), K$_2$CO$_3$ (26.3 mg, 0.19 mmol, 2.0 equiv, 75 °C for 2 h. Purified by flash
chromatography using (DCM to 3% MeOH/DCM) to obtain a white solid (51.0 mg, 88%) as the desired product ($R_f = 0.32$ in 5% MeOH/DCM). M.p. 123.0-125.0 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.98-7.86 (m, 4H), 7.54-7.46 (m, 3H), 7.41-7.32 (m, 4H), 6.18 (d, $J = 8.6$ Hz, 1H), 5.62 (dd, $J = 10.9$, 9.6 Hz, 1H), 5.36 (t, $J = 9.9$ Hz, 1H), 5.02 (d, $J = 3.6$ Hz, 1H), 4.87-4.77 (m, 1H), 4.64-4.55 (m, 1H), 4.50-4.42 (m, 1H), 4.22 (dd, $J = 11.9$, 4.4 Hz, 1H), 3.63-3.55 (m, 1H), 2.96-2.86 (m, 1H), 2.72-2.61 (m, 1H), 2.30-2.21 (m, 1H), 2.01-1.93 (m, 1H), 1.91 (s, 3H), 1.63-1.48 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.3, 170.2, 167.2, 165.5, 148.6, 133.6, 133.5, 129.91, 128.87, 128.8, 128.7, 128.5, 128.4, 120.6, 97.2, 71.0, 70.4, 69.1, 68.6, 64.5, 52.8, 50.0, 33.7, 28.2, 24.7, 23.2, 23.1; HRMS m/z calcd for C$_31$H$_{34}$N$_4$O$_9$Na $[M + Na]^+$ 629.2218, found 629.2222.

**Synthesis of compound 13b (LM26):** Compound 11b (100.0 mg, 0.12 mmol, 1.0 equiv), DMF (10.0 mL), K$_2$CO$_3$ (34.3 mg, 0.24 mmol, 2.0 equiv), 75 °C for 5 h. Purified by flash chromatography (DCM to 5% MeOH/DCM) to obtain a white solid (60.0 mg, 76%) as the desired product ($R_f = 0.29$ in 5% MeOH/DCM). M.p. 108.0-110.0 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.97-7.87 (m, 4H), 7.54-7.45 (m, 3H), 7.41-7.31 (m, 4H), 6.21 (d, $J = 9.1$ Hz, 1H, -NH), 5.62 (dd, $J = 10.9$, 9.5 Hz, 1H, H-3), 5.37 (t, $J = 9.8$ Hz, 1H, H-4), 4.99 (d, $J = 3.6$ Hz, 1H, H-1), 4.72-4.67 (m, 2H, -O-CH$_2$-CH$_2$-N), 4.59-4.50 (m, 1H, H-2), 4.22-4.02 (m, 3H, H-6a, H-6b, -O-CH$_a$-CH$_2$-N), 4.00-3.93 (m, 1H, -O-CH$_b$-CH$_2$-N), 3.87-3.78 (m, 1H, H-5), 2.90-2.71 (m, 2H, -HC=C-CH$_2$-CH$_2$-), 2.16-1.98 (m, 2H, -OOC-CH$_2$-CH$_2$-), 1.90 (s, 3H), 1.80-1.68 (m, 1H), 1.67-1.55 (m, 1H), 1.54-1.40 (m, 2H), 1.28-1.07 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.3, 170.1, 167.0, 165.3, 148.5 (HC=C-), 133.5, 129.83, 128.79, 128.7, 128.44, 128.42, 120.8 (HC=C-), 97.3 (C-1), 71.1 (C-3), 70.4 (C-4), 68.5 (C-5), 67.1 (-O-CH$_2$-CH$_2$-N), 64.1 (C-6), 52.3 (C-2), 49.6 (-O-CH$_2$-CH$_2$-N), 32.9,
27.9, 27.4, 25.9, 24.7, 23.7, 23.1; HRMS m/z calcd for C$_{33}$H$_{38}$N$_{2}$O$_{9}$Na $[M + Na]^+$ 657.2531, found 657.2529.

**Synthesis of compound 14a (LM34):** Compound 12a (96.0 mg, 0.12 mmol, 1.0 equiv), DMF (10.0 mL), K$_2$CO$_3$ (33.5 mg, 0.24 mmol, 2.0 equiv), 75 °C for 2 h. Purified by flash chromatography (DCM to 3% MeOH/DCM) to obtain a colorless liquid which turns into a white solid over time (66.3 mg, 88%) as the desired product ($R_f = 0.2$ in 5% MeOH/DCM). M.p. 117.0-118.0 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.97-7.85 (m, 4H), 7.54-7.45 (m, 2H), 7.42-7.31 (m, 5H), 5.88 (d, $J = 9.2$ Hz, 1H), 5.65 (t, $J = 10.2$ Hz, 1H), 5.31 (t, $J = 9.6$ Hz, 1H), 4.93 (d, $J = 3.6$ Hz, 1H), 4.75-4.66 (m, 1H), 4.57-4.42 (m, 2H), 4.19-4.01 (m, 3H), 3.55-3.37 (m, 2H), 2.90-2.70 (m, 2H), 2.43-2.16 (m, 4H), 1.87 (s, 3H), 1.79-1.72 (m, 2H), 1.69-1.62 (m, 2H), 1.53-1.45 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.4, 169.9, 167.2, 165.3, 147.3, 133.5, 129.9, 129.8, 128.7, 128.5, 121.2, 97.4, 71.4, 69.5, 68.6, 64.8, 64.0, 52.3, 46.6, 41.0, 34.3, 29.8, 27.3, 24.4, 23.3, 23.2; HRMS m/z calcd for C$_{32}$H$_{36}$N$_{2}$O$_{9}$Na $[M + Na]^+$ 643.2375, found 643.2374.

**Synthesis of compound 14b (LM36):** Compound 12b (86.0 mg, 0.10 mmol, 1.0 equiv), DMF (10.0 mL), K$_2$CO$_3$ (28.9 mg, 0.20 mmol, 2.0 equiv), 75 °C for 2 h. Purified by flash chromatography (DCM to 3% MeOH/DCM) to obtain a white solid (56.6 mg, 83%) as the desired product ($R_f = 0.2$ in 5% MeOH/DCM). M.p. 97.0-98.0 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.98-7.86 (m, 4H), 7.53-7.46 (m, 2H), 7.40-7.31 (m, 5H), 5.95 (d, $J = 9.1$ Hz, 1H), 5.67 (t, $J = 10.2$ Hz, 1H), 5.35 (t, $J = 9.7$ Hz, 1H), 4.98 (d, $J = 3.6$ Hz, 1H), 4.69-4.60 (m, 1H), 4.55-4.48 (m, 1H), 4.47-4.39 (m, 1H), 4.24-4.09 (m, 3H), 3.66-3.51 (m, 2H), 2.86-2.68 (m, 2H), 2.43-2.24 (m, 2H), 2.08 (t, $J = 7.0$ Hz, 2H), 1.88 (s, 3H), 1.74-1.64 (m, 2H), 1.61-1.47 (m, 2H), 1.33-1.16 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.2, 169.9, 167.2, 165.4, 148.1, 133.53, 133.51, 130.0, 129.84, 128.79, 128.7, 128.46, 128.45, 120.9, 98.0, 71.4, 70.0, 68.5, 65.5, 63.8, 52.6, 46.6, 32.4, 30.3, 27.4,
26.6, 25.7, 24.6, 23.5, 23.2; HRMS m/z calcd for C$_{34}$H$_{40}$N$_4$O$_9$Na [M + Na]$^+$ 671.2688, found 671.2686.

**Synthesis of compound 14c (LM38):** Compound 12c (90.0 mg, 0.10 mmol, 1.0 equiv), DMF (10.0 mL), K$_2$CO$_3$ (30.4 mg, 0.20 mmol, 2.0 equiv), 75 ºC for 2 h. Purified by flash chromatography (DCM to 2% MeOH/DCM) to obtain a white solid (59.5 mg, 83%) as the desired product (R$_f$ = 0.32 in 5% MeOH/DCM). M.p. 87.0-89.0 ºC; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.97-7.88 (m, 4H), 7.54-7.47 (m, 2H), 7.41-7.31 (m, 5H), 6.12 (d, $J$ = 8.8 Hz, 1H), 5.62 (t, $J$ = 10.6 Hz, 1H), 5.44 (t, $J$ = 9.8 Hz, 1H), 4.91 (d, $J$ = 3.6 Hz, 1H), 4.61-4.42 (m, 3H), 4.33-4.12 (m, 3H), 3.71-3.61 (m, 1H), 3.46-3.36 (m, 1H), 2.88-2.71 (m, 2H), 2.33-2.04 (m, 4H), 1.93 (s, 3H), 1.75-1.68 (m, 4H), 1.56-1.47 (m, 2H), 1.28-1.15 (m, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.4, 170.2, 167.2, 165.4, 133.52, 133.47, 129.9, 129.8, 128.8, 128.5, 128.4, 121.3, 97.7, 71.4, 70.2, 68.0, 65.0, 63.2, 52.6, 46.6, 33.7, 30.2, 28.20, 28.19, 28.14, 27.7, 27.2, 24.9, 24.4, 23.1; HRMS m/z calcd for C$_{36}$H$_{44}$N$_4$O$_9$Na [M + Na]$^+$ 699.3001, found 699.3000.

Compounds 15a-b and 16a-b were prepared similarly as compound 8a.

**Synthesis of compound 15a:** Compound 7c (200.0 mg, 0.31 mmol, 1.0 equiv), t-BuOH: THF: H$_2$O (v:v:v 1:1:1, 3.0 mL), 10d (89.2 mg, 0.4 mmol, 1.3 equiv), CuSO$_4$·5H$_2$O (15.5 mg, 0.062 mmol, 0.2 equiv), NaAsc (24.6 mg, 0.124 mmol, 0.4 equiv), 24 h. Purified by flash chromatography (DCM to 3% MeOH/DCM) to obtain a yellowish slurry (209.0 mg, 78%) as the desired product (R$_f$ = 0.5 in 5% MeOH/DCM). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.86-7.80 (m, 4H), 7.68 (d, $J$ = 8.3 Hz, 2H), 7.54-7.46 (m, 2H), 7.45 (s, 1H), 7.41 (s, 1H), 7.38-7.29 (m, 4H), 7.20 (d, $J$ = 8.0 Hz, 2H), 6.26 (d, $J$ = 9.1 Hz, 1H), 5.54 (t, $J$ = 10.8 Hz, 1H), 5.28 (t, $J$ = 9.6 Hz, 1H), 4.84 (d, $J$ = 3.6 Hz, 1H), 4.63-4.55 (m, 4H), 4.49-4.42 (m, 1H), 4.20-4.04 (m, 4H), 3.89-3.83 (m, 1H), 2.91 (t, $J$ = 6.2 Hz, 2H), 2.76-2.66 (m, 4H), 2.34 (s, 3H), 1.82 (s, 3H), 1.75-1.62 (m, 4H); $^{13}$C NMR
(100 MHz, CDCl₃) δ 172.6, 171.0, 166.7, 165.1, 148.2, 147.3, 145.1, 133.6, 133.4, 132.3, 129.9, 129.81, 129.75, 128.7, 128.6, 128.4, 128.0, 122.2, 121.6, 97.5, 71.2, 68.9, 68.6, 68.2, 66.7, 51.9, 49.6, 45.9, 35.1, 28.5, 28.3, 25.2, 25.0, 22.8, 21.6. HRMS m/z calcd for C₄₂H₄₇N₇O₁₂SNa [M + Na]+ 896.2896, found 896.2886.

**Synthesis of compound 15b:** Compound 7c (100.0 mg, 0.15 mmol, 1.0 equiv), t-BuOH: THF: H₂O (v:v:v 1:1:1, 3.0 mL), 10e (46.8 mg, 0.19 mmol, 1.3 equiv), CuSO₄·5H₂O (7.3 mg, 0.03 mmol, 0.2 equiv), NaAsc (12.3 mg, 0.06 mmol, 0.4 equiv), 24 h. Purified by flash chromatography (DCM to 2% MeOH/DCM) to obtain a yellowish slurry (108.0 mg, 79%) as the desired product (Rf = 0.41 in 5% MeOH/DCM). ¹H NMR (400 MHz, CDCl₃) δ 7.88-7.81 (m, 4H), 7.69 (d, J = 8.3 Hz, 2H), 7.54-7.47 (m, 2H), 7.45 (s, 1H), 7.40 (s, 1H), 7.38-7.30 (m, 4H), 7.21 (d, J = 7.9 Hz, 2H), 6.11 (d, J = 9.1 Hz, 1H), 5.53 (t, J = 10.8 Hz, 1H), 5.28 (t, J = 9.6 Hz, 1H), 4.86 (d, J = 3.6 Hz, 1H), 4.64-4.58 (m, 4H), 4.50-4.42 (m, 1H), 4.21-4.07 (m, 4H), 3.93-3.86 (m, 1H), 2.91 (t, J = 6.2 Hz, 2H), 2.73-2.65 (m, 4H), 2.35 (s, 3H), 1.83 (s, 3H), 1.70-1.59 (m, 4H), 1.36-1.28 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 172.5, 170.8, 166.8, 165.1, 148.4, 147.5, 145.1, 133.6, 133.5, 132.3, 129.83, 129.77, 128.7, 128.6, 128.4, 128.0, 122.2, 121.6, 97.5, 71.2, 68.9, 68.7, 68.2, 66.6, 51.9, 49.6, 45.8, 35.1, 29.0, 28.4, 28.0, 25.3, 25.0, 22.9, 21.6. HRMS m/z calcd for C₄₃H₄₉N₇O₁₂SNa [M + Na]+ 910.3052, found 910.3043.

**Synthesis of compound 15c:** To a 50 mL RBF, compound 9 (100.0 mg, 0.15 mmol, 1.0 equiv), t-BuOH: THF: H₂O (v:v:v 1:1:1, 3.0 mL), 10d (43.1 mg, 0.19 mmol, 1.3 equiv), CuSO₄·5H₂O (7.3 mg, 0.03 mmol, 0.2 equiv), NaAsc (12.3 mg, 0.06 mmol, 0.4 equiv), 16 h. Purified by flash chromatography (DCM to 5% MeOH/DCM) to obtain a yellowish slurry (116.0 mg, 87%) as the desired product (Rf = 0.41 in 5% MeOH/DCM). ¹H NMR (400 MHz, CDCl₃) δ 7.91-7.85 (m, 4H), 7.68 (d, J = 8.3 Hz, 2H), 7.56-7.46 (m, 2H), 7.43 (s, 1H), 7.40-7.31 (m, 5H),
7.20 (d, J = 8.1 Hz, 2H), 6.39 (d, J = 9.1 Hz, 1H), 5.59 (t, J = 9.7 Hz, 1H), 5.31 (t, J = 9.7 Hz, 1H),
4.84 (d, J = 3.5 Hz, 1H), 4.68-4.56 (m, 3H), 4.54-4.42 (m, 2H), 4.33-4.24 (m, 1H), 4.20-4.07 (m, 2H), 3.86-3.78 (m, 1H), 3.34-3.26 (m, 1H), 2.88 (t, J = 5.9 Hz, 2H), 2.78-2.66 (m, 4H), 2.35 (s, 3H), 2.32-2.16 (m, 2H), 1.94 (s, 3H), 1.80-1.59 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.2, 166.9, 165.2, 148.3, 147.3, 145.0, 133.5, 133.4, 132.3, 129.9, 129.8, 128.8, 128.7, 128.4, 128.0, 122.4, 120.9, 97.5, 71.4, 69.1, 68.6, 68.4, 64.8, 52.1, 46.8, 46.0, 35.4, 29.7, 28.5, 28.3, 25.04, 24.96, 23.0, 21.6. HRMS m/z calcd for C$_{43}$H$_{49}$N$_7$O$_{12}$SNa [M + Na]$^+$ 910.3052, found 910.3043.

**Synthesis of compound 15d:** Compound 9 (100.0 mg, 0.15 mmol, 1.0 equiv), t-BuOH:
THF: H$_2$O 1:1:1 (v:v:v 1:1:1, 3.0 mL), 10e (45.9 mg, 0.19 mmol, 1.3 equiv), CuSO$_4$$\cdot$5H$_2$O (7.3 mg, 0.03 mmol, 0.2 equiv), NaAsc (11.9 mg, 0.06 mmol, 0.4 equiv), 16 h. Purified by flash chromatography (DCM to 5% MeOH/DCM) to obtain a yellowish slurry (113.0 mg, 83%) as the desired product ($R_f$ = 0.46 in 5% MeOH/DCM). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.90-7.84 (m, 4H), 7.69 (d, J = 8.3 Hz, 2H), 7.56-7.45 (m, 2H), 7.44-7.30 (m, 6H), 7.21 (d, J = 8.2 Hz, 2H), 6.36 (d, J = 9.1 Hz, 1H), 5.59 (t, J = 9.7 Hz, 1H), 5.31 (t, J = 9.7 Hz, 1H), 4.84 (d, J = 3.5 Hz, 1H), 4.66-4.57 (m, 3H), 4.54-4.46 (m, 2H), 4.31-4.25 (m, 1H), 4.20-4.08 (m, 2H), 3.87-3.80 (m, 1H), 3.38-3.20 (m, 1H), 2.90 (t, J = 6.0 Hz, 2H), 2.73-2.65 (m, 4H), 2.35 (s, 3H), 2.32-2.19 (m, 2H), 1.93 (s, 3H), 1.73-1.59 (m, 4H), 1.36-1.25 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.8, 167.0, 165.2, 148.6, 147.5, 145.0, 133.54, 133.46, 132.3, 129.9, 129.8, 128.8, 128.7, 128.4, 128.0, 122.2, 121.0, 97.5, 71.5, 69.1, 68.6, 68.4, 64.8, 52.0, 47.0, 45.9, 35.2, 29.9, 29.0, 28.4, 28.0, 25.2, 25.0, 23.0, 21.6. HRMS m/z calcd for C$_{44}$H$_{51}$N$_7$O$_{12}$SNa [M + Na]$^+$ 924.3209, found 924.3213.

Compounds 16a-d, 22, 24 were prepared similarly as for compound 13c. Amount of all chemicals, reaction time, yield, $R_f$ value and characterization of the product are listed, respectively.
The macrocycles were typically obtained first as a clear waxy liquid which upon standing for a few days turned to a white solid.

**Synthesis of compound 16a (DM24):** Compound 15a (75.0 mg, 0.085 mmol, 1.0 equiv), DMF (12.0 mL), K$_2$CO$_3$ (23.7 mg, 0.17 mmol, 2.0 equiv), 85 °C for 4.0 h. The crude was purified by flash chromatography (DCM to 2% MeOH/DCM) to obtain a white solid (54.0 mg, 90%) as the desired product ($R_f = 0.14$ in 5% MeOH/DCM). The reaction was also carried out using CH$_3$CN as the solvent: Compound 15a (50.0 mg, 0.05 mmol, 1.0 equiv) was dissolved in CH$_3$CN (12.0 mL), then K$_2$CO$_3$ (15.8 mg, 0.11 mmol, 2.0 equiv) was added, the reaction mixture was stirred at 75 °C for 11.0 h. The solvent was removed using a rotavap, and the crude was purified using flash column similarly. The pure compound was obtained in 77% yield, 31.0 mg. m.p. 127.0-129.0 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.94-7.86 (m, 4H), 7.54-7.44 (m, 2H), 7.39-7.32 (m, 5H), 7.30 (s, 1H), 5.96 (d, $J = 9.3$ Hz, 1H), 5.55 (t, $J = 10.8$ Hz, 1H), 5.38 (t, $J = 9.9$ Hz, 1H), 4.73 (d, $J = 3.5$ Hz, 1H), 4.70-4.58 (m, 4H), 4.51-4.43 (m, 1H), 4.21-4.14 (m, 1H), 4.13-4.00 (m, 3H), 3.88-3.78 (m, 1H), 3.02-2.93 (m, 1H), 2.89-2.82 (m, 1H), 2.80-2.70 (m, 2H), 2.66-2.53 (m, 2H), 1.92 (s, 3H), 1.67-1.55 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.3, 170.1, 166.8, 165.2, 148.8, 147.9, 133.6, 133.4, 129.8, 129.7, 128.8, 128.7, 128.5, 128.4, 121.6, 120.7, 98.2, 70.9, 69.2, 68.1, 66.9, 62.8, 51.9, 50.3, 45.5, 34.8, 27.7, 24.8, 24.7, 23.2; HRMS m/z calcd for C$_{35}$H$_{39}$N$_7$O$_9$Na [M + Na]$^+$ 724.2701, found 724.2704.

**Synthesis of compound 16b (DM25):** Compound 15b (68.0 mg, 0.07 mmol, 1.0 equiv), DMF (12.0 mL), K$_2$CO$_3$ (21.2 mg, 0.15 mmol, 2.0 equiv), 80 °C for 2.0 h. Purified by flash chromatography (DCM to 2% MeOH/DCM) to obtain a white solid (48.0 mg, 88%) as the desired product ($R_f = 0.2$ in 5% MeOH/DCM). The reaction was also carried out in acetonitrile: compound 15b (50.0 mg, 0.05 mmol, 1.0 equiv), CH$_3$CN (10.0 mL), K$_2$CO$_3$ (15.6 mg, 0.11 mmol, 2.0 equiv),
75 °C for 14.0 h, yield 28.5 mg, 71%. M.p. 239.0-240.0 °C; ^1H NMR (400 MHz, CDCl₃) δ 7.92-7.85 (m, 4H), 7.62 (s, 1H), 7.54-7.47 (m, 2H), 7.46 (s, 1H), 7.39-7.30 (m, 4H), 5.91 (d, J = 9.3 Hz, 1H), 5.56 (t, J = 9.5 Hz, 1H), 5.30 (t, J = 9.9 Hz, 1H), 4.67 (d, J = 3.5 Hz, 1H), 4.65-4.55 (m, 4H), 4.51-4.45 (m, 1H), 4.36-4.30 (m, 1H), 4.16-4.08 (m, 2H), 4.02-3.95 (m, 1H), 3.93-3.87 (m, 1H), 3.03-2.90 (m, 2H), 2.79-2.70 (m, 4H), 1.91 (s, 3H), 1.75-1.66 (m, 4H), 1.32-1.25 (m, 2H); ^13C NMR (100 MHz, CDCl₃) δ 170.1, 169.9, 166.9, 165.4, 148.2, 147.6, 133.6, 133.5, 129.83, 129.81, 128.8, 128.6, 128.4, 122.2, 121.6, 97.9, 71.2, 69.6, 68.6, 66.8, 63.4, 52.0, 49.6, 45.2, 34.3, 27.5, 27.3, 26.1, 24.5, 23.2; HRMS m/z calcd for C₃₆H₄₁N₇O₉Na [M + Na]^+ 738.2858, found 738.2862.

**Synthesis of compound 16c (DM34):** Compound 15c (120.0 mg, 0.13 mmol, 1.0 equiv), DMF (15.0 mL), K₂CO₃ (37.3 mg, 0.27 mmol, 2.0 equiv), 75 °C for 2.0 h. Purified by flash chromatography (DCM to 3% MeOH/DCM) to obtain a white solid (82.0 mg, 85%) as the desired product, R_f = 0.21 in 5% MeOH/DCM. The reaction was also carried out in acetonitrile: Compound 15c (50.0 mg, 0.05 mmol, 1.0 equiv), CH₃CN (8.0 mL), K₂CO₃ (15.7 mg, 0.11 mmol, 2.0 equiv), 75 °C for 14.0 h, yield 31.5 mg, 78%, m.p. 99.0-101.0 °C; ^1H NMR (400 MHz, CDCl₃) δ 7.93-7.89 (m, 4H), 7.54-7.47 (m, 2H), 7.39-7.34 (m, 6H), 6.09 (d, J = 8.8 Hz, 1H), 5.54 (t, J = 10.6 Hz, 1H), 5.46 (t, J = 9.6 Hz, 1H), 4.77 (d, J = 3.7 Hz, 1H), 4.60-4.44 (m, 5H), 4.33-4.26 (m, 1H), 4.17-4.03 (m, 2H), 3.59-3.49 (m, 1H), 3.30-3.21 (m, 1H), 2.83-2.70 (m, 6H), 2.33-2.20 (m, 2H), 1.94 (s, 3H), 1.80-1.69 (m, 2H), 1.69-1.59 (m, 2H); ^13C NMR (100 MHz, CDCl₃) δ 170.3, 170.1, 167.1, 165.3, 148.2, 147.8, 133.6, 133.5, 129.9, 129.7, 128.8, 128.76, 128.5, 128.4, 121.7, 121.2, 97.7, 71.3, 69.7, 67.7, 64.8, 63.2, 52.4, 46.4, 45.4, 34.8, 29.6, 28.0, 25.1, 24.8, 23.1; HRMS m/z calcd for C₃₆H₄₁N₇O₉Na [M + Na]^+ 738.2858, found 738.2855.
Synthesis of compound 16d (DM35): Compound 15d (90.0 mg, 0.099 mmol, 1.0 equiv), DMF (12.0 mL), K$_2$CO$_3$ (27.5 mg, 0.19 mmol, 2.0 equiv), 80 °C for 3.0 h. The crude was purified by flash chromatography (DCM to 3% MeOH/DCM) to obtain a white solid upon standing (57.0 mg, 78%) as the desired product ($R_f = 0.26$ in 5% MeOH/DCM). The reaction was also carried out using CH$_3$CN as the solvent: Compound 15d (50.0 mg, 0.05 mmol, 1.0 equiv), CH$_3$CN (8.0 mL), K$_2$CO$_3$ (15.3 mg, 0.11 mmol, 2.0 equiv), 75 °C for 15.0 h, 30.0 mg of product was obtained in 74%. M.p. 92.0-94.0 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.94-7.89 (m, 4H), 7.55-7.46 (m, 2H), 7.42 (s, 1H), 7.41 (s, 1H), 7.38-7.32 (m, 4H), 6.10 (d, $J = 9.0$ Hz, 1H), 5.57 (t, $J = 9.6$ Hz, 1H), 5.40 (t, $J = 9.8$ Hz, 1H), 4.84 (d, $J = 3.7$ Hz, 1H), 4.61-4.44 (m, 5H), 4.36-4.28 (m, 1H), 4.25-4.15 (m, 2H), 3.76-3.65 (m, 1H), 3.44-3.33 (m, 1H), 2.99-2.81 (m, 2H), 2.80-2.73 (m, 2H), 2.73-2.67 (m, 2H), 2.36-2.23 (m, 2H), 1.93 (s, 3H), 1.74-1.65 (m, 4H), 1.34-1.27 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.3, 169.8, 167.0, 165.4, 148.3, 147.7, 133.6, 133.5, 129.9, 129.8, 128.8, 128.7, 128.5, 128.4, 122.0, 121.4, 97.6, 71.5, 69.7, 68.4, 65.6, 63.7, 52.3, 46.9, 45.3, 34.5, 29.9, 28.1, 27.8, 26.7, 24.8, 24.8, 23.1; HRMS m/z calcd for C$_{37}$H$_{43}$N$_7$O$_9$Na [M + Na]$^+$ 752.3014, found 752.3011.

Synthesis of compound 18: To a 50 mL RBF, compound 17 (200.0 mg, 0.54 mmol, 1.0 equiv) was dissolved in AcOH: H$_2$O (v:v 4:1, 5.0 mL) and heated at 75 °C for 4 h. The reaction was stopped, and solvent was dried under vacuum to afford the crude, which was purified by flash chromatography using eluent from pure DCM to 3% MeOH/DCM to obtain a colorless liquid (129 mg, 85%) as the desired product ($R_f = 0.3$ in 10% MeOH/DCM). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.97 (d, $J = 8.4$ Hz, 1H), 4.99 (d, $J = 5.6$ Hz, 1H), 4.80 (d, $J = 5.7$ Hz, 1H), 4.56 (d, $J = 3.5$ Hz, 1H), 4.50 (t, $J = 6.0$ Hz, 1H), 3.87-3.77 (m, 2H), 3.73-3.61 (m, 2H), 3.52-3.40 (m, 2H), 3.35-3.31 (m, 1H), 3.25 (s, 3H), 3.18-3.10 (m, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 167.5, 97.7, 72.7,
Synthesis of compound 19: In a 50 mL RBF, compound 18 (500 mg, 1.80 mmol, 1.0 equiv) was taken and dissolved in pyridine (5.0 mL). To this solution, tosyl chloride (258.8 mg, 1.35 mmol, 2.5 equiv) dissolved in pyridine (5.0 mL) was added dropwise at 0 °C. The reaction was monitored in 1.5 h to see full conversion. Pyridine was dried under vacuum and crude was coated on silica gel and isolated by flash chromatography using eluent from pure DCM to 2% MeOH/DCM to obtain a sticky colorless slurry (628 mg, 81%) as the desired product (Rf = 0.51 in 10% MeOH/DCM). 1H NMR (400 MHz, CDCl3) δ 7.80 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 6.63 (d, J = 9.0 Hz, 1H), 4.63 (d, J = 3.7 Hz, 1H), 4.36-4.27 (m, 2H), 4.11-3.99 (m, 3H), 3.78-3.71 (m, 1H), 3.67 (t, J = 9.6 Hz, 1H), 3.49 (t, J = 9.4 Hz, 1H), 3.35 (s, 3H), 3.06 (br s, 2H), 2.44 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 168.3, 145.0, 132.8, 129.9, 128.0, 98.2, 73.4, 70.6, 70.0, 69.0, 55.4, 53.3, 52.4, 21.6. LC-MS (ESI+) calcd for C16H22N4O8 [M + H]+ 431.1, found 431.1.

Synthesis of compound 20: In a 50 mL RBF, compound 19 (628 mg, 1.45 mmol, 1.0 equiv), pyridine (3.0 mL) and benzoyl chloride (0.42 mL, 4.37 mmol, 3.0 equiv) was added at 0 °C dropwise and let it stir for 1.5 h to see full conversion. The reaction mixture was extracted with DCM (25.0 mL) and washed with NH4Cl (10.0 mL) and NaHCO3 (10.0 mL) followed by brine (10.0 mL). The organic layer was then dried over anhydrous Na2SO4 and concentrated under reduced pressure to obtain the crude. Crude was purified by flash chromatography using eluent from pure Hexanes to 40% EtOAc/Hexanes to obtain a colorless liquid (850 mg, 91%) as the desired product (Rf = 0.35 in 40% EtOAc/Hexanes). 1H NMR (400 MHz, CDCl3) δ 7.91-7.81 (m, 4H), 7.72 (d, J = 8.3 Hz, 2H), 7.55-7.45 (m, 2H), 7.39-7.31 (m, 4H), 7.22 (d, J = 8.0 Hz, 2H), 6.63 (d, J = 9.4 Hz, 1H), 5.56 (dd, J = 10.8, 9.5 Hz, 1H), 5.36 (t, J = 9.6 Hz, 1H), 4.78 (d, J = 3.5 Hz,
1H), 4.50-4.42 (m, 1H), 4.23-4.16 (m, 2H), 4.15-4.09 (m, 1H), 3.85 (d, J = 16.6 Hz, 1H), 3.73 (d, J = 16.6 Hz, 1H), 3.45 (s, 3H), 2.37 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.72, 166.69, 165.1, 144.9, 133.52, 133.46, 132.5, 129.9, 129.7, 128.7, 128.6, 128.4, 128.0, 98.0, 71.3, 68.8, 68.1, 68.1, 55.7, 52.5, 52.2, 21.6. LC-MS (ESI+) calcd for C$_{30}$H$_{31}$N$_4$O$_{10}$S [M + H]$^+$ 639.2, found 639.2.

**Synthesis of compound 21:** To a 50 mL RBF, compound 20 (110.0 mg, 0.17 mmol, 1.0 equiv) in $t$-BuOH: THF: H$_2$O (v:v:v 1:1:1, 3.0 mL) and 10-undecynoic acid 10c (40.8 mg, 0.22 mmol, 1.3 equiv), CuSO$_4$·5H$_2$O (8.6 mg, 0.034 mmol, 0.2 equiv), NaAsc (13.7 mg, 0.06 mmol, 0.4 equiv) and Tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (TBTA) (15.9 mg, 0.03 mmol, 0.2 equiv) was added and the reaction mixture was stirred at rt for 7 h. The reaction was stopped, and solvent was dried under vacuum to afford the crude, which was purified by flash chromatography using eluent from pure DCM to 2% MeOH/DCM to obtain white solid (95 mg, 67%) as the desired product (R$_f$ = 0.5 in 5% MeOH/DCM). M.p. 74.5-77.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.89-7.79 (m, 4H), 7.71 (d, J = 8.3 Hz, 2H), 7.54-7.47 (m, 2H), 7.38-7.32 (m, 4H), 7.21 (d, J = 7.9 Hz, 2H), 7.11 (s, 1H), 6.20 (d, J = 9.3 Hz, 1H), 5.54-5.48 (m, 1H), 5.34 (t, J = 9.6 Hz, 1H), 4.91 (d, J = 16.5 Hz, 1H), 4.83 (d, J = 16.5 Hz, 1H), 4.74 (d, J = 3.6 Hz, 1H), 4.49-4.41 (m, 1H), 4.22-4.09 (m, 3H), 3.40 (s, 3H), 2.72-2.61 (m, 2H), 2.36 (s, 3H), 2.33 (t, J = 7.4 Hz, 2H), 1.69-1.54 (m, 4H), 1.36-1.29 (m, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 178.4, 178.1, 166.5, 165.5, 165.0, 149.0, 144.9, 133.5, 132.5, 129.9, 129.8, 128.61, 128.58, 128.5, 128.4, 128.0, 121.9, 97.8, 71.5, 68.7, 68.1, 68.0, 55.8, 52.6, 52.4, 33.91, 33.88, 29.1, 29.01, 28.97, 28.96, 28.93, 28.89, 28.87, 28.6, 28.4, 25.5, 24.71, 24.66, 21.6, 18.4. LC-MS (ESI+) calcd for C$_{41}$H$_{49}$N$_4$O$_{12}$S [M + H]$^+$ 821.3, found 821.4.

**Synthesis of compound 23:** To a 50 mL RBF, compound 20 (100 mg, 0.16 mmol, 1.0 equiv) was taken in THF: H$_2$O: $t$-BuOH (v:v:v 1:1:1, 3.0 mL). To this solution, 10d (46.0 mg, 0.20
mmol, 1.3 equiv), CuSO₄·5H₂O (7.8 mg, 0.03 mmol, 0.2 equiv) and NaAsc (12.4 mg, 0.06 mmol, 0.4 equiv) were added and the reaction mixture was stirred at room temperature for 12 h. The reaction was stopped, and solvent was dried under vacuum to afford the crude, which was purified by flash chromatography using pure eluent from pure DCM to 2% DCM/MeOH to obtain a white solid (112 mg, 83%) as the desired product (R_f =0.27 in 5% MeOH/DCM). M.p. 93.5-95.5 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.84-7.77 (m, 4H), 7.70 (d, J = 8.3 Hz, 2H), 7.53-7.44 (m, 3H), 7.37-7.28 (m, 4H), 7.20 (d, J = 8.1 Hz, 2H), 7.14 (br s, 1H), 6.60 (d, J = 8.7 Hz, 1H), 5.55 (t, J = 10.3 Hz, 1H), 5.37 (t, J = 9.7 Hz, 1H), 4.99-4.84 (m, 2H), 4.77 (d, J = 3.3 Hz, 1H), 4.66-4.57 (m, 2H), 4.49-4.42 (m, 1H), 4.21-4.15 (m, 2H), 4.14-4.08 (m, 1H), 3.39 (s, 3H), 2.92 (t, J = 5.3 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 2.62-2.53 (m, 2H), 2.34 (s, 3H), 1.72-1.47 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 166.5, 165.7, 165.0, 148.3, 147.1, 145.0, 133.6, 132.4, 129.81, 129.76, 129.7, 128.6, 128.53, 128.45, 128.4, 128.0, 122.6, 122.3, 97.8, 71.6, 68.6, 68.0, 55.8, 52.5, 52.4, 45.9, 34.9, 28.3, 27.7, 24.9, 24.8, 21.6. LC-MS (ESI+) calcd for C₄₁H₄₆N₇O₁₂S [M + H]^+ 860, found 860.

**Synthesis of compound 22 (C2ML):** To a 50 mL RBF, compound 21 (70.0 mg, 0.09 mmol, 1.0 equiv), DMF (14.0 mL) and K₂CO₃ (23.54 mg, 0.17 mmol, 2.0 equiv), 75 °C, 2 h. Purification by flash chromatography (DCM to 1% MeOH/DCM) to obtain a white solid, (79%, 44 mg). R_f = 0.64 in 5% MeOH/DCM. M.p. 207.5-210.0 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.98-7.88 (m, 4H), 7.55-7.48 (m, 3H), 7.41-7.34 (m, 4H), 5.55 (d, J = 9.3 Hz, 1H), 5.42-5.34 (m, 2H), 4.98 (d, J = 16.0 Hz, 1H), 4.80 (d, J = 16.0 Hz, 1H), 4.47-4.27 (m, 4H), 3.91-3.81 (m, 1H), 3.37 (s, 3H), 2.84 (t, J = 6.1 Hz, 2H), 2.29-2.07 (m, 2H), 1.78-1.67 (m, 2H), 1.67-1.49 (m, 2H), 1.39-1.19 (m, 8H); ¹³C NMR (100 MHz, CDCl₃) δ 173.3, 166.6, 166.0, 165.6, 149.6, 133.5, 129.9, 129.8, 129.7, 129.0, 128.9, 128.5, 128.4, 122.5, 97.8, 72.6, 70.2, 68.7, 62.4, 56.0, 53.4, 52.3, 34.2,
31.5, 30.4, 29.9, 29.6, 28.7, 25.4, 25.0. LC-MS (ESI+) calcd for C\textsubscript{34}H\textsubscript{41}N\textsubscript{4}O\textsubscript{9} [M + H]\textsuperscript{+} 649, found 649.

**Synthesis of compound 24 (C2DLM):** To a 50 mL RBF, Compound 23 (75.0 mg, 0.08 mmol, 1.0 equiv), K\textsubscript{2}CO\textsubscript{3} (24.1 mg, 0.17 mmol, 2.0 equiv), DMF (10.0 mL), 70 °C, 2.0 h. Purification by flash chromatography (DCM to 2% MeOH/DCM) to obtain a white solid (46 mg, 77 %) as the desired product. R\textsubscript{f} = 0.4 in 5% MeOH/DCM. M.p. 83.5-85.0 °C; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 8.03-7.97 (m, 2H), 7.96-7.91 (m, 2H), 7.54-7.48 (m, 3H), 7.47 (s, 1H), 7.42-7.33 (m, 4H), 5.31-5.21 (m, 2H), 5.16 (t, J = 9.9 Hz, 1H), 5.09 (d, J = 16.8 Hz, 1H), 4.73-4.64 (m, 2H), 4.56-4.49 (m, 1H), 4.47 (d, J = 4.1 Hz, 1H), 4.38-4.27 (m, 3H), 3.56-3.47 (m, 1H), 3.07 (s, 3H), 2.99-2.92 (m, 2H), 2.88-2.69 (m, 4H), 2.06-1.95 (m, 2H), 1.77-1.68 (m, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 169.9, 166.7, 165.7, 165.4, 149.3, 148.8, 133.5, 133.4, 132.1, 130.0, 129.9, 128.86, 128.85, 128.5, 128.4, 122.8, 97.4, 72.7, 70.0, 68.6, 63.6, 55.5, 53.1, 51.8, 50.4, 33.9, 29.8, 27.1, 26.1, 25.3. LC-MS (ESI+) calcd for C\textsubscript{34}H\textsubscript{38}N\textsubscript{7}O\textsubscript{9} [M + H]\textsuperscript{+} 688, found 688.

**Macrolactonization using Na\textsubscript{2}CO\textsubscript{3} as the base:** To a 50 mL RBF, compound 23 (100.0 mg, 0.11 mmol, 1.0 equiv), Na\textsubscript{2}CO\textsubscript{3} (24.6 mg, 0.23 mmol, 2.0 equiv), DMF (12 mL), 70 °C, 2.0 h. After solvent was removed, the crude was purified by flash chromatography (DCM to 5% MeOH/DCM) to obtain the monolactone compound 24 as a white solid (66 mg, 83 %).

**Macrolactonization using Cs\textsubscript{2}CO\textsubscript{3} as the base:** To a 50 mL RBF, compound 23 (100.0 mg, 0.11 mmol, 1.0 equiv), Cs\textsubscript{2}CO\textsubscript{3} (75.8 mg, 0.23 mmol, 2.0 equiv), DMF (12 mL), 70 °C, 2.0 h. After solvent was removed, the crude was purified by flash chromatography (DCM to 5% MeOH/DCM) to obtain the dimeric macrodilactone compound 25 as a white solid (41 mg, 51 %). R\textsubscript{f} = 0.32 in 5% MeOH/DCM). M.p. 257.0-258.0 °C; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.97-7.87 (m, 4H), 7.57-7.46 (m, 3H), 7.43-7.32 (m, 5H), 5.54 (d, J = 9.2 Hz, 1H), 5.35-5.28 (m, 1H), 5.24 (t, J
= 9.9 Hz, 1H), 4.93 (d, \( J = 16.2 \text{ Hz}, 1H \)), 4.83 (d, \( J = 16.2 \text{ Hz}, 1H \)), 4.67-4.51 (m, 2H), 4.38-4.25 (m, 4H), 3.70-3.62 (m, 1H), 3.01-2.90 (m, 5H), 2.89-2.71 (m, 4H), 2.07-1.92 (m, 2H), 1.83-1.71 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 170.7, 166.5, 165.7, 165.6, 149.2, 147.3, 133.6, 133.4, 129.88, 139.85, 128.9, 128.7, 128.5, 128.4, 122.3, 121.8, 97.4, 72.2, 69.7, 68.3, 63.6, 55.3, 53.4, 52.0, 45.5, 34.8, 29.4, 27.6, 26.1, 25.2. LC-MS (ESI+) calcd for C\(_{68}\)H\(_{74}\)N\(_{14}\)O\(_{18}\)Na [M + Na]\(^+\) 1398 found 1398.

2.4.2 GENERAL METHOD FOR THE CYCLOADDITION REACTIONS OF SUGAR AZIDE WITH ALKYNES

The screening reactions were carried out in a Heidolph carousel 12 plus reaction station system with 20 mL glass vessels. The click test reactions were performed using the apparatus under nitrogen atmosphere at controlled temperatures using similar method as described. Control experiments without macrocycles were carried out in the same batch under the same conditions with other reactions. The reaction vessel was flushed with nitrogen, about 40.0 mg of the sugar azide 17 was added to then macrocycles were then added, followed by 1.0 mL of ethanol and the corresponding alkynes (1.2 to 1.5 equiv), followed by addition of 1.0 mL CuSO\(_4\) aqueous solution and lastly NaAsc. The reaction vessel was capped, and nitrogen balloon was used to maintain the reaction under nitrogen atmosphere. The reaction was set to stir at 1000 rpm and temperature was set at 30.0 °C. CuSO\(_4\)·5H\(_2\)O (54.0 mg) was dissolved in 10.0 mL of DI water (degassed) to prepare the stock solution for reactions of 40.0 mg of the azide for phenyl acetylene; and 27.0 mg of CuSO\(_4\)·5H\(_2\)O was dissolved in 10 mL of DI water (degassed) to make the stock solution for 1-octyne. After the reaction, the solvent was removed under reduced pressure to obtain the crude. The crude obtained was purified by flash column chromatography using DCM to 2% MeOH/DCM as eluent.
CHAPTER 3
SYNTHESIS AND CHARACTERIZATION OF PHOTO-RESPONSIVE MOLECULES

3.1 INTRODUCTION

Photochromic molecules have found applications in several areas such as data storage, fluorescence microscopy and optical sensing. Some of the commonly used photochromic units are cis-trans functional groups (azobenzene), photo switchable groups (spiropyrans and diarylethenes) and photodimerizable or polymerizable groups (coumarins, anthracenes). Figure 48 shows the example of photochromic units. Azobenzene and stilbenes are used as photochromic units due to their cis-trans isomerization property. Dithienylethenes can be used for their ring opening and closing nature with different wavelengths. Coumarins can homodimerize with a wavelength of >280 nm.

Figure 48. Examples of photochromic molecules.

Coumarins are widely used as the substrate for photodegradation. They also have different therapeutic applications in breast cancer (Benzo-α-pyrones), skin disorders known as Mycosis,
(Psoralen, Angelicin), leukemia (Umbelliferon), anticoagulant (Warfarin).\textsuperscript{86} 7-Aminocoumarin analogue (Figure 49, compound 1) works as an inhibitor of thioredoxin reductases which shows high antitumor activity ($IC_{50} = 3.6 \ \mu M$).\textsuperscript{132} By introducing a piperidine ring with linker in 7-position (Figure 49, compound 2), coumarins have significant activity against some viruses like Marburg virus ($IC_{50} = 0.5 \ \mu M$) or Ebolavirus ($IC_{50} = 1.2 \ \mu M$).\textsuperscript{133} Beside antitumor and antibacterial activities, coumarin derivatives also have antioxidant,\textsuperscript{134,135} anti-inflammatory\textsuperscript{136} and anticoagulant activities.\textsuperscript{137} Compound 3 in Figure 49 is one of the example showing anti-inflammatory activity.\textsuperscript{136} Compound 4 (Figure 49) has found its activity as enzyme inhibitor ($IC_{50} = 3.87 \ \text{mM}$) by inhibiting aldehyde dehydrogenase 1A1.\textsuperscript{138}

![Figure 49. Structures of coumarin derivatives for pharmacological application.](image)

Besides these, fluorescent properties of coumarin makes it very versatile for photochemical applications.\textsuperscript{89} There are research where the coumarin-dipeptide gelator are made by photodimerization by different UV irradiation. The UV irradiation of 365 nm helped in the
stacking of the gelators. Other study shows that there are photodegradable hydrogels with coumarin moiety which can be degraded by the irradiation of UV light of 365 nm. We can see from these two distinct examples that the coumarin molecule with different type of linkage can be used to degrade the gels or stack up the gels with the same wavelength of UV light. Another sugar-based coumarin hydrogelator was also photo-cleaved by UV light of 320 nm to give the supramolecular gelator. This unique example of galactose based coumarin was introduced to cancer cell and the cell death was induced by intracellular self-assembly triggered by light.

Click reaction has been utilized as the bridge to connect pyranose scaffold with coumarin fluorophore. The bis-triazolyl groups between pyranose and coumarin served as the chelation site. These glycoconjugates showed the selectivity towards specific ions. This ion selectivity was dependent on the structure of coumarin fluorophore. 7-hydroxyl-coumarin linked to glucosides and galactosides (Figure 50, compound 5 and 6) showed the fluorescence quenching with the addition of Ag⁺ ion. The fluorescence quenching was not observed with other control studies done with other metals ions like Al³⁺, Pb²⁺, Na⁺, Mg²⁺, K⁺, Ca²⁺, Ba²⁺, Cu²⁺, Co²⁺, Cd²⁺, Mn²⁺, Ni²⁺ and Zn²⁺. Coumarin has also been used as fluorescent probes with the presence of triazole moiety. The click reaction of the azido group (Figure 50, compounds 7, 8 and 9) turns on the fluorescence property of this coumarin derivative. The starting azido methane group doesn’t have fluorescence property or have very weak fluorescence intensity. After the click reaction, with new triazole functional group, there is significant increase in fluorescence intensity. There was also significant red shift in wavelength with the range of 432 – 459 nm.
Diarylethene compounds are popular for their photochromic properties due to its photochromic reversibility. The diarylethenes undergo ring-opening and closing while they are under UV or visible light respectively. These types of ring closure won’t get affected by the thermal conditions and are resistance to fatigue. The property of the photochromic molecules can be changed by substituting different groups with halogen in the heterocyclic ring. Diarylethenes (DTE) have been utilized to obtain fluorescent molecular switches, photo-sensitive polymers, photo-conductive devices and liquid-crystalline materials. They have found applications in the formation of LMWGs. Some examples of the DTE-based organogelators are shown in Figure 51. Different strengths of organogelators were obtained in aromatic solvents for gelator 10, which contains one DTE unit. Both open and closed isomers of gelator 10 were good gelators. Gel to sol transition of gelator 11 in water was also reported which can be triggered by UV irradiation. Fluorinated disodium salt 12 also showed good gelation properties in organic
solvents and also possessed gel to sol transition upon photoirradiation.\textsuperscript{154} Another research has shown that the weakening of gel was observed after irradiation of UV light of 313 nm and was attributed to the ring closure.\textsuperscript{155} These gelation properties were affected by intramolecular and intermolecular H-bonding of amide units as well as alkyl substituents for compound 13. Structure 13 contains two DTE units which are connected by xylylene spacer and contains four amide units to promote the hydrogen bonding.

Figure 51. Diarylethene based LMWGs.
Carbohydrates are one of the most abundant and renewable natural resources which have very interesting properties. They have multiple chiral centers that can be used as the heterogeneous catalyst used for the enantioselective reactions. The LMWG’s have a wide range of application in the field of biomedicine, enzyme immobilization, tissue engineering, drug delivery, organocatalyst, etc. Different LMWGs can be used as the drug delivery carriers, the release of drug can be triggered by different factors like pHs where the desired gelator might be made by acid or base sensitive functional groups, enzymatic process can also be used to exploit both the degradation and the controlled assembly of hydrogel materials. Light can also be used to trigger gel formation of gel to solution transitions through photodegradation of the gelators.

Motivated by these recent developments and to explore the photoresponsive properties of coumarin based carbohydrates, here we report the rational design of different coumarin scaffolds. In this study, we are interested in the synthesis of different coumarin containing sugar derivatives for their variety of applications, especially for uses in forming self-assembling gelators and as fluorescence probes, besides these several diarylethene derivatives were also synthesized for the preparation of photo-switchable nanomaterials.

3.2 RESULTS AND DISCUSSIONS

Coumarin derivatives have shown numerous applications especially as fluorescent probes for biological applications. We are interested in designing coumarin derivatives with interesting fluorescent properties. In this study, a series of coumarin derivatives have been synthesized. The library of coumarin intermediates were synthesized by following literature procedures. To explore the photochemical activities, we proposed to synthesize different
coumarin based sugar derivatives. To make different sugar derivatives we started to make a library of different coumarin intermediates as shown in the Figure 52.

In this work we have synthesized ten different coumarin glycoconjugates with different functional groups. Out of ten derivatives, nine of them are glucosamine based and only compound 32 is glucose based coumarin glycoconjugates. Functional groups like amide, esters, triazoles are inserted in the system to explore the gelation properties of coumarin glycoconjugates with different functional groups. The coumarin glycoconjugates with different substituents in coumarin moieties has shown gelation behavior. We also have studied their UV-vis and fluorescence properties, these compounds can have potential applications as fluorescence probes.

Figure 52. Structures of different coumarin intermediates.
Different coumarin and sugar derivatives have been synthesized. As shown in Scheme 5, compounds 23 and 24 were prepared by SN2 reaction from compound 22. The two derivatives were tested for their gelation properties in several solvents, unfortunately, both compounds didn’t form gels in those solvents as shown in Table 4. Compounds 23 and 24 were not soluble in most of the solvents. To change the behavior of the coumarin derivatives, we proposed and synthesized four different analogs of triazole based molecules. Click reaction was used to introduce triazole functional group to the amide linked glucosamine derivative (scheme 6). Azido precursor 26 was reported from our lab,64 which was used to make compound 27-30 using CuSO4.5H2O and sodium ascorbate. We also synthesized coumarin glycoconjugates from anomeric azide of tetraacetyl glucose (Scheme 7). The reaction was accomplished by click reaction using Cu(I) and DIEA. Glucose azide was reacted with coumarin alkyne (16). All these compounds were tested for gel properties (Table 4).

Another amide derivative directly linked with coumarin-3-position and C2 carbon of glucosamine was also synthesized by coupling glucosamine 33 with coumarin-3-carboxylic acid to obtain compound 34 (Scheme 8). We prepared compound 36 (scheme 8) as a new sugar-based derivative from carboxylic acid precursor 35 by SN2 reaction displacing chloride from compound 20.
Scheme 5. Coumarin linked sugar derivatives synthesized by $S_N2$ reaction.
Scheme 6. Coumarin linked sugar derivatives synthesized by click reactions, C2 position.

Scheme 7. Synthesis of anomeric triazoles containing coumarin glycoconjugates.
Scheme 8. Synthesis of amide and ester derivatives with different coumarin intermediates.

The gelation properties of all coumarin glycoconjugates are summarized in Table 4. The gelation properties were tested in different solvents like hexanes (Hex), toluene (Tol), isopropanol (IPA), ethanol (EtOH), water (H₂O), mixture of dimethyl sulfoxide (DMSO) and water with 1:1 and 1:2 ratio and mixture of ethanol and water with 1:1 and 1:2 ratio. The glycoconjugates with amide liked triazoles derivatives were not good gelators, compound 27 being the exception which formed gels with MGC of 2.5 mg/mL in DMSO: H₂O (1:2). These coumarin derivatives showed
gelation behavior towards the mixture of organic and water as solvent. Compound 28 made G20 in toluene and all other amide linked triazole derivatives didn’t form any gels. But the result for derivative 32, which contains triazoles in the anomeric position, was slightly different. Most of them formed gels in several solvent systems, especially mixture of organic and aqueous solvent. The gels made by anomeric triazoles based systems were mostly G10 or G20 with exception of compound 32, which formed gels in ethanol and ethanol water (1:2) at 6.7 mg/mL.

Table 4. Gelation results for coumarin glycoconjugates.

<table>
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<tr>
<th>Cpd</th>
<th>Hex</th>
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<th>EtOH</th>
<th>H2O</th>
<th>DMSO: H2O (1:1)</th>
<th>DMSO: H2O (1:2)</th>
<th>EtOH: H2O (1:1)</th>
<th>EtOH: H2O (1:2)</th>
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<td>I</td>
<td>G 10.0&lt;sub&gt;o&lt;/sub&gt;</td>
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<td>G 5&lt;sub&gt;o&lt;/sub&gt;</td>
<td>I</td>
<td>G 10&lt;sub&gt;o&lt;/sub&gt;</td>
<td>P</td>
<td>G20&lt;sub&gt;o&lt;/sub&gt;</td>
<td>UG</td>
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G, gel at room temperature; the number in the table are the minimum gelation concentrations in mg/mL; I, insoluble; P, precipitate; UG, unstable gel; S, soluble at 20 mg/mL; UG, unstable gel.
Compound 27 was able to form gel in DMSO: H₂O (1:2). The optical micrograph for this compound shows small fibers. Under UV light (320 nm), this compound glows, while remained white opaque gel under natural light, before and after irradiation of UV light. This gel was not affected or degraded by exposing to UV light for 24 h (Figure 53). Compound 36 formed gel in EtOH with minimum gelation concentration of 5.0 mg/mL. The gel formed is opaque (Figure 54), the optical micrograph of compound 36 didn’t show any fibrous network.

Figure 53: Photos for the gels formed by compound 27 in DMSO: H₂O (1:2) with 3.3 mg/mL; (A) Image of gel under natural light, (B) under UV (320 nm) light, (C) optical micrograph (scale bar; 50 µm).
The fluorescence spectra of coumarins and their glycoconjugates were measured by exciting the solution of respective compounds in 10^{-5} M EtOH. The \( \lambda_{\text{max}} \) obtained from UV spectra was used as the excitation wavelength for this study. Their photophysical properties are summarized and included in Table 5. Some of the coumarin glycoconjugates showed increase in fluorescence intensity compared to their coumarin starting material. This property was observed in compound 27 with a little bathochromic shift. Using the same excitation wavelength (\( \lambda_{\text{ex}} \)) of 324 nm, the fluorescence intensity also increased twice compared to its alkyne precursor 6 (Figure 55). We can assume that this increased intensity was contributed by the triazole functional group after the click reaction. Likewise, compound 36 at \( \sim 345 \) nm has about 7 times increased emission intensity compared to its chloro precursor, compound 20 (Figure 57).

Another coumarin glycoconjugate 24 showed significantly increased intensity at 290 nm, which was about 14 times higher than its acid precursor (Figure 56), 17. Compound 24 showed hypsochromic shift after reacting with coumarin precursor. The increased fluorescence intensity
of these molecules can be utilized to study the fluorescence lifetime. This property can be used for studying biomolecules and their molecular association.

Table 5. Photophysical properties of coumarins and their glycoconjugates

<table>
<thead>
<tr>
<th>Code</th>
<th>Coumarins</th>
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Figure 55. Fluorescent spectra of compounds 14 and 27, the $\lambda_{\text{ex}} = 324$ nm.

Figure 56. Fluorescent spectra of compounds 17 and 24, the $\lambda_{\text{ex}} = 290$ nm.
3.2.1 SYNTHESIS OF DITHIENYLETHENES-BASED PHOTOCHROMIC MOLECULES

Beside coumarin-based photochromic molecules, we also synthesized diarylethene-based photochromic molecules. Synthesis of compound 42 was done by following the experimental procedure from literatures, with slight modifications (Scheme 9). The commercially available glutaric acid (37) was converted into glutaryl chloride (38) using thionyl chloride and catalytic amount of DMF. The glutaryl chloride was then reacted with 2-chloro-5-methyl thiophene (compound 39) to afford the electrophilic aromatic substituted product, 40. Compound 40 underwent McMurry cyclization using Zn and TiCl₄ to obtain the advanced intermediate compound 41. Compound 41 was functionalized after a chlorine-lithium exchange reaction. The

Figure 57. Fluorescent spectra of compounds 20 and 36, the λex = 346 nm.
lithiated intermediate is further converted into diacid, 42, by using dry ice. The monoester of 42 was also synthesized using methyl iodide and sodium bicarbonate as compound 43.

Compound 42 was further converted to its acid chloride followed by thioacid derivative by using sodium hydrosulfide in ethanol as solvent. This compound 44 was unstable so it was converted to its potassium salt, 45. The compound 44 and 45 have been utilized for the formation of photo switchable quantum dots through collaboration with Prof. Choi’s lab at UVA.162

These photochromic molecules show the fatigue resistance and they are thermally stable.\textsuperscript{150} These derivatives can be switched from open to closed ring isomers with particular wavelength of light and the closed ring form are believed to be stable for more than 1000 years at 30 °C.\textsuperscript{163} This property of diarylethenes makes them possible candidates for optical data storage and also as biomarkers to probe biological events.\textsuperscript{150,151,163-165}

For the future plan, we plan to synthesize the thiol-based compound (49, Scheme 10). Advanced intermediates for this system have been synthesized starting from compound 41. Compound 41 was lithiated followed by reacting with DMF to obtain dialdehyde product 46. The reduction of 46 with NaBH\textsubscript{4} was gave the alcohol intermediate, 47. The tosylation of compound 47 to obtain 48 was attempted, but the tosylated compound seem to be unstable and compound 48 was not isolated. Further troubleshooting of this step and evaluation of alternate route to get the desired product 49 is currently under investigation.

Scheme 10. Synthesis of thiol based photochromic molecules.
3.2.2 SELECTED NMR SPECTRA AND FTIR SPECTRA

Figure 58. $^1$H NMR and $^{13}$C NMR spectra of compound 18 in d$_6$-DMSO.
Figure 59. $^1$H NMR and $^{13}$C NMR spectra of compound 27 in d$_6$-DMSO.
Figure 60. $^1$H NMR and $^{13}$C NMR spectra of compound 36 in CDCl$_3$. 
Figure 61. $^1$H and $^{13}$C NMR spectra of compound 42 in DMSO-d$_6$. 
Figure 62. IR spectra of compound 27 and 36.
3.3 CONCLUSION

In summary, we have synthesized several novel N-acetyl-D-glucosamine and coumarin based compounds through S\textsubscript{N}2 reactions as well as utilizing click chemistry. Few of these glycoconjugates showed the gelation property. One of the triazole derivative with glucosamine gave MGC of 2.5 mg/mL in DMSO: H\textsubscript{2}O (1:2). The fluorescence properties of these coumarin glycoconjugates were studied and we found that few of the coumarin derivatives have a significant increase in fluorescence intensity after they are attached with the sugar molecules. Future studies can be done for the exploration of light triggered coumarin-linked sugar derivatives.

3.4 EXPERIMENTAL SECTION

**General Procedure:** All reactions were carried out under normal condition (1 atm pressure, without catalyst unless otherwise mentioned, rt or heated with specified temperature), reagents and solvents were obtained from commercial suppliers from Sigma-Aldrich, VWR, and Fisher and used directly without any purifications. All reactions unless otherwise noted were carried out in oven dried glassware under nitrogen atmosphere. All purification was conducted by flash chromatography using 230-400 mesh silica gel with a gradient of solvent systems. Thin-layer chromatography (TLC) analysis was performed with aluminum backed TLC plates (Sigma-Aldrich) with UV and fluorescence indicator and visualized using UV lamp at 254 nm then stained with PMA solution. \textsuperscript{1}H NMR and proton-decoupled \textsuperscript{13}C NMR spectra were obtained with Bruker 400 MHz spectrometers in DMSO-\textit{d}_6 or CDCl\textsubscript{3}. The chemical shifts were reported using CDCl\textsubscript{3}/DMSO-\textit{d}_6 as internal standard at 7.26/2.50 ppm and at 77.0/39.5 ppm, respectively. 2D NMR experiments (HSQC, COSY) were also conducted to assist the compound characterizations. COSY spectra were used for characterizing the sugar protons as they usually appear between 3-5
ppm. After characterizing each proton, HSQC can be used to characterize the carbon NMR spectra. Melting point measurements were carried out using a Fisher Jones melting point apparatus. UV-vis analysis were performed using Shimadzu UV Spectrophotometer (UV-1800) and Fluorescence spectra were obtained using Shimadzu Spectro Fluorophotometer (RF-6000) with single scan mode, slit width of 1.0 nm and scan speed of 600 nm/min. The IR spectra were obtained using a Bruker Platinum ATR (Alpha) FT-IR Spectrometer, the parameters are resolution: 4 cm⁻¹, 64 scans.

**Gelation testing:** 2 mg of the compounds were tested in a 1-dram vial with a screw cap. To this vial, solvents were added in a 0.1 mL increment, which gives the starting concentration of 20 mg/mL was used. The mixture was heated to dissolve the sample, the sample were occasionally sonicated if required to make them fully dissolved. The mixture was then allowed to cool at room temperature. If the homogenous semi-solid sample was observed then, the vial was then inverted to see the formation of gel. It can be called gel if the solvents are all trapped, and no flow of solvent is observed. If the gel like material falls apart, then it is unstable gel. If the stable gel is formed, 0.1 mL increments of solvent is further added until the gel is unstable. The minimum gelation concentration (MGC) is obtained with the maximum volume of solvent that the sample can form stable gel at.

**Synthesis of compound 15:** To a solution of Coumarin-3-carboxylic acid (50 mg, 0.26 mmol, 1 equiv), Propargyl alcohol (0.016 mL, 0.26 mol, 1 equiv), N, N-dicyclohexyl carbodiimide (59.0 mg, 0.286 mmol, 1.1 equiv), and 4-dimethylaminopyridine (3.18 mg, 0.026 mmol, 0.1 equiv) in dichloromethane (2 mL) was stirred at room temperature for 6 h. After 6 h, the precipitated N, N-dicyclohexylurea was filtered off and the filtrate was washed with water, 5% acetic acid, and again with water. It was then dried over sodium sulphate and the solvent was evaporated. The
residue obtained was further purified by column chromatography (hexanes to 40% EtOAc/Hexanes) to afford the ester (55 mg, 92%).

**Synthesis of compound 16**: To a 50 mL RBF (oven dried), propargyl amine (0.015 mL, 0.24 mmol, 1 equiv), K₂CO₃ (99 mg, 0.72 mmol, 3 equiv) was added to DCM (anh, 3 mL) and stirred for half an hour at 0 °C. To this reaction mixture, acid chloride of compound 1 (54.6 mg, 0.26 mmol, 1.1 equiv) diluted in 1 mL of DCM was added dropwise in the period of 10 mins and let the reaction stir for 4 h with gradual increase in temperature form 0 °C to rt. After 4 h, reaction was monitored by ¹H NMR to see the desired peaks. The reaction mixture was diluted with DCM (10 mL) and quenched by 5% NaHCO₃ (5 mL). The mixture was let stir for 15 mins and the extraction was done using separatory funnel. The collected organic layer was dried by anhydrous Na₂SO₄ and solvent was removed under vacuum. The resulting crude was purified using column (pure DCM to 3% MeOH/DCM) to obtain desired product as yellowish solid. Rf (0.6 in 5% MeOH/DCM), Yield 82% (49 mg).

**Synthesis of compound 17**: To a 50 mL RBF (oven dried), 5-bromo salicylaldehyde (500 mg, 2.48 mmol, 1 equiv), Meldrum’s acid (358.49 mg, 2.48 mmol, 1 equiv) and sodium azide (80.85 mg, 1.24 mmol, 0.5 equiv) was added along with 10 mL of DI H₂O. The reaction mixture was stirred vigorously for 20 h at rt. Then the mixture solution was treated with cold 10 mL of 0.1 M HCl keeping the reaction mixture at ice bath. ¹H NMR was checked after filtering and washing the solid with water to observe the product formation. The desired product was yellow solid. Yield: 90% (602 mg).

**Synthesis of compound 18**: To a 50 mL RBF (oven dried), propargyl amine (0.07 mL, 1.12 mmol, 1 equiv), K₂CO₃ (464.38 mg, 3.36 mmol, 3 equiv) was added to DCM (anh, 6 mL) and stirred for half an hour at 0 °C. To this reaction mixture acid chloride of compound 4 (320.6 mg, 1.12 mmol, 1.1 equiv) diluted in 1.0 mL of DCM was added dropwise in the period of 10 mins and let the reaction stir for 4 h with
gradual increase in temperature form 0 °C to rt. After 4 h, reaction was monitored by $^1$H NMR to see the desired peaks. The reaction mixture was diluted with DCM (10 mL) and quenched by 5% NaHCO$_3$ (10 mL). The mixture was let stir for 15 mins and the extraction was done using separatory funnel. The collected organic layer was dried by anhydrous Na$_2$SO$_4$ and solvent was removed under vacuum. The resulting crude was purified using column (pure DCM to 3% MeOH/DCM) to obtain desired product as yellowish solid. Rf (0.48 in 5% MeOH/DCM), Yield 85% (261 mg). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.91 (t, $J =$ 5.6, 1H), 8.83 (s, 3H), 8.26 (d, $J =$ 2.4 Hz, 1H), 7.89 (dd, $J =$ 3.8 Hz, 1H), 7.48 (d, $J =$ 8.9 Hz, 1H), 4.11 (dd, $J =$ 2.7 Hz, 2H), 3.15 (t, $J =$ 2.5 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 160.7, 159.6, 152.9, 146.4, 136.3, 132.1, 120.3, 119.8, 118.4, 116.6, 80.6, 73.2, 28.7.

**Synthesis of compound 20:** 4-methoxy phenol (100 mg, 0.8 mmol, 1.0 equiv) was dissolved in H$_2$SO$_4$ (2.5 mL) at 0 °C, then ethyl 4-chloroacetoacetate (1.23 mL, 0.8 mmol, 1.0 equiv) was added slowly at 0 °C and let it warm up slowly overnight. After 14 h, TLC showed the reaction was complete. The mixture was then poured into ice-water (3 mL) and the solid was filtered and washed with water (2 mL X 2). The solid was triturated with Hexanes to obtain compound (product) (120.5 mg, 67% yield) as yellowish solid.

**Synthesis of compound 23:** To a 100 mL RBF, compound 22 (102.2, 0.25 mmol, 1.0 equiv), coumarin 3- carboxylic acid (72.5 mg, 0.38 mmol, 1.5 equiv) and 0.12 mL of DIEA (0.13 mL, 0.76 mmol, 3.0 equiv) was added along with 3.0 mL of DMF and stir bar. The mixture was stirred for 5 h at rt. The reaction was monitored by $^1$H NMR showing the formation of product but incomplete reaction. Then the reaction was let to stir for 19 h more. The reaction was monitored again by $^1$H NMR showing the completion of reaction. Then the reaction mixture was diluted adding cold water and filtered using Hirch funnel and washed with water. The white solid was seen in the funnel which was the desired product confirmed by $^1$H NMR. Then the solid was further dried using oil pump. Yield: 83% (110.2 mg). $^1$H NMR (400 MHz, d$_6$-DMSO) δ 8.87 (s, 1H), 8.14
(d, J = 8.5 Hz, 1H), 7.96 (q, J = 3.1 Hz, 1H), 7.81-7.74 (m, 1H), 7.49-7.41 (m, 4H), 7.40-7.35 (m, 3H), 5.62 (s, 1H), 5.26 (d, J = 5.6, 1H), 4.78 (q, J = 12.5 Hz, 2H), 4.67 (d, J = 3.6 Hz, 1H), 4.18 (q, J = 4.9 Hz, 1H), 3.94-3.86 (m, 1H), 3.78-3.68 (m, 2H), 3.67-3.66 (m, 1H) 3.52 (t, J = 9.2 Hz, 1H), 3.32 (s, 3H); $^{13}$C NMR (100 MHz, d$_6$-DMSO) δ 166.5, 161.9, 156.1, 154.6, 149.7, 137.7, 134.8, 130.4, 128.8, 128.0, 126.4, 124.9, 117.7, 116.9, 116.2, 100.9, 98.6, 81.7, 67.9, 67.4, 62.8, 62.5, 54.9, 54.1.

**Synthesis of compound 24:** To a 50 mL RBF, compound 22 (50 mg, 0.12 mmol, 1 equiv), bromo coumarin 3-carboxylic acid (36.8 mg, 0.19 mmol, 1.5 equiv) and DIEA (64.5 µL, 0.37 mmol, 3.0 equiv) was added along with 4 mL of DMF and stir bar. The reaction was stirred at rt for 14 h to see conversion above 95%. The reaction was stopped, and solvent was dried. The crude further purified using column chromatography (DCM to 2% MeOH/DCM). Yield: 72% (53 mg).

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.57 (s, 1H), 7.81- 7.76 (m, 3H), 7.50 - 7.47 (m, 2H), 7.38- 7.34 (m, 3H), 7.28 (d, J = 8.7, 1H), 5.56 (s, 1H), 4.92 - 4.82 (m, 3H), 4.31 - 4.20 (m, 2H), 4.13 (t, J = 9.6 Hz, 1H), 3.91 - 3.85 (m, 1H), 3.78 (t, J = 10.2 Hz, 1H), 3.61 (t, J = 9.2 Hz, 1H), 3.43 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.6, 161.8, 156.7, 154.1, 149.1, 137.7, 137.2, 131.9, 129.2, 128.3, 126.4, 119.2, 118.6, 118.4, 117.9, 102.1, 98.8, 82.1, 69.7, 69.0, 63.8, 62.4, 55.6, 54.3.

**Synthesis of compound 25:** To a 50 mL RBF, 22 (100.0 mg, 0.25 mmol, 1.0 equiv) in DMF (2.0 mL), and K$_2$CO$_3$ (68.7 mg, 0.49 mmol, 2.0 equiv) was added and stirred for 30 mins. After 30 minutes, coumarin azide 33 (60.6 mg, 0.30 mmol, 1.2 equiv) was added to the solution at and let it stir for 4.0 h heating at 50 °C. After 4.0 h the starting material was disappeared. The reaction was diluted adding DCM, quenched by adding 5 mL of 5% NaHCO$_3$. The compound was extracted using DCM (3 X 10). The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated by reduced pressure to obtain crude. The crude was further purified by column chromatography
using eluent from pure DCM to 3.0% DCM/MeOH. to obtain yellow solid as desired compound. Yield 74 % (96 mg)

Synthesis of compound 27: Compound 26 (100 mg, 0.27 mmol, 1 equiv) was dissolved in THF: H2O: t-BuOH (4.5 mL). To this solution, compound 19 (72.4 mg, 0.36 mmol, 1.3 equiv) was added, followed by adding CuSO4 (8.8 mg, 0.055 mmol, 0.2 equiv) and L-Ascorbic acid sodium salt (21.7 mg, 0.11 mmol, 0.4 equiv). The reaction mixture was stirred for 24 h at rt. After complete disappearance of starting material as indicated by TLC or 1H NMR spectroscopy, solvent was removed under reduced pressure. The crude product was purified by column chromatography using eluent from pure Hexanes to 60% EtOAc/Hexanes to obtain an off-white solid which came out along with another UV active compound along with desired. This obtained compound was further triturated with DCM to obtain 63 mg (40%) of desired compound. The filtrate was further purified by column using DCM to 2% MeOH/DCM to obtain 55 mg of compound. Total yield: 76% (118 mg). 1H NMR (400 MHz, DMSO-d6) δ 8.51 (d, J = 8.5, 1H), 8.22 (s, 1H), 7.99 (d, J = 9.4, 1H), 8.68 (d, J = 8.7, 1H), 7.49-7.43 (m, 2H), 7.42-7.33 (m, 3H), 7.17 (d, J = 2.4, 1H), 7.03 (q, J = 3.7, 1H), 6.30 (d, J = 9.5, 1H), 5.32 (d, J = 5.6, 1H), 5.28 (s, 2H), 5.28 (s, 2H), 5.19 (d, J = 1.2, 2H), 4.66 (d, J = 3.6, 1H), 4.23-4.15 (m, 1H), 3.91-3.83 (m, 1H), 3.78-3.69 (m, 2H), 3.68-3.59 (m, 1H), 3.52 (t, J = 9.2, 1H), 3.33 (s, 3H); 13C NMR (100 MHz, DMSO-d6) δ 165.5, 161.1, 160.2, 155.3, 144.2, 141.6, 137.7, 129.5, 128.8, 128.0, 126.4, 112.9, 112.6, 112.5, 101.5, 100.9, 98.5, 81.7, 67.9, 67.5, 62.5, 61.6, 54.8, 54.4, 51.5.

Synthesis of compound 28: Compound 26 (50 mg, 0.14 mmol, 1 equiv) was dissolved in THF: H2O: t-BuOH (1:1:1, 2 mL). To this solution, compound 15 (40.7 mg, 0.18 mmol, 1.3 equiv) was added, followed by adding CuSO4 (4.4 mg, 0.027 mmol, 0.2 equiv) and L-Ascorbic acid sodium salt (10.9 mg, 0.055 mmol, 0.4 equiv). The reaction mixture was stirred for 36 h to see
about 90% conversion. The reaction was stopped, solvent was air dried, and the crude was loaded in the column. The pure compound eluted with 5% MeOH/DCM to give yield of 68% (55 mg). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.78 (s, 1H), 8.51 (d, $J$ = 8.5 Hz, 1H), 8.19 (s, 1H), 7.93 (dd, $J$ = 7.8 and 1.5 Hz, 1H), 7.76-7.72 (m, 1H), 7.47-7.42 (m, 3H), 7.41-7.36 (m, 3H), 5.62 (s, 1H), 5.39 (s, 2H), 5.19 (d, $J$ = 1.1 Hz, 2H), 4.66 (d, $J$ = 3.6 Hz, 1H), 4.18 (q, $J$ = 4.8 Hz, 1H), 3.89-3.84 (m, 1H), 3.77-3.70 (m, 2H), 3.68-3.60 (m, 1H), 3.68-3.60 (m, 1H), 3.52 (t, $J$ = 9.2 Hz, 1H), 3.33 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.5, 162.2, 155.8, 154.6, 149.1, 141.2, 137.7, 134.6, 130.4, 128.8, 128.0, 126.5, 126.4, 124.8, 117.7, 117.1, 116.1, 100.9, 98.5, 81.7, 67.9, 67.5, 62.5, 58.2, 54.2, 54.8, 54.4, 51.5.

**Synthesis of compound 29:** Compound 26 (100 mg, 0.27 mmol, 1 equiv) was dissolved in CH$_3$CN (3.0 mL). To this solution, coumarin 16 (81.1 mg, 0.36 mmol, 1.3 equiv) was added, followed by adding CuI (10.5 mg, 0.055 mmol, 0.2 equiv) and DIEA (0.1 mL, 0.55 mmol, 2.0 equiv) was added and stirred at rt. The reaction mixture was stirred for 24 h at rt and monitored by $^1$H NMR to see consumption of starting sugar and new peaks. The reaction was stopped, solvent dried under vacuum and crude was purified using column (pure DCM to 5% MeOH/DCM) to obtain yellowish solid as desired compound. (73% yield, 118 mg). $^1$H NMR (400 MHz, d$_6$-DMSO) $\delta$ 9.13 (t, $J$ = 5.6 Hz, 1H), 8.91 (s, 1H), 8.48 (d, $J$ = 8.5 Hz, 1H), 8.01 - 7.97 (m, 2H), 7.78- 7.73 (m, 1H), 7.51 (d, $J$ = 8.4 Hz, 1H), 7.46 - 7.42 (m, 3H), 7.39 - 7.36 (m, 3H), 5.61 (s, 1H), 5.30 (d, $J$ = 5.6 Hz, 1H), 5.18 - 5.09 (m, 2H), 4.65 (d, $J$ = 3.6 Hz, 1H), 4.61 (d, $J$ = 5.6 Hz, 2H), 4.18 (q, $J$ = 4.9 Hz, 1H), 3.88 - 3.83 (m, 1H), 3.77 - 3.60 (m, 3H), 3.51 (t, $J$ = 9.2 Hz, 1H), 3.32 (s, 3H); $^{13}$C NMR (100 MHz, d$_6$-DMSO) $\delta$ 165.5, 161.0, 160.3, 153.9, 147.6, 143.8, 137.7, 134.1, 130.3, 128.8, 128.0, 126.3, 125.1, 124.4, 118.7, 118.4, 116.1, 100.9, 98.5, 81.7, 67.9, 67.5, 54.8, 54.4, 51.4, 34.8.
Synthesis of compound 30: Compound 26 (100 mg, 0.27 mmol, 1 equiv) was dissolved in CH$_3$CN (3.0 mL). To this solution, coumarin 18 (109.2 mg, 0.36 mmol, 1.3 equiv) was added, followed by adding CuI (10.5 mg, 0.055 mmol, 0.2 equiv) and DIEA (0.1 mL, 0.55 mmol, 2.0 equiv) was added and stirred at rt. The reaction mixture was stirred for 24 h at room temperature and monitored by $^1$H NMR to see consumption of starting sugar and new peaks. The reaction was stopped, solvent dried under vacuum and crude was purified using column (pure DCM to 5% MeOH/DCM) to obtain yellowish solid as desired compound. (60% yield, 110 mg). $^1$H NMR (400 MHz, d$_6$-DMSO) $\delta$ 9.09 (t, $J$ = 5.6 Hz, 1H), 8.85 (s, 1H), 8.48 (d, $J$ = 8.5 Hz, 1H), 8.27 (d, $J$ = 2.4 Hz, 1H), 7.96 (s, 1H), 7.89 (q, $J$ = 3.8 Hz, 1H), 7.49 - 7.43 (m, 3H), 7.39 - 7.35 (m, 3H), 5.61 (s, 1H), 5.14 (d, $J$ = 2.1 Hz, 2H), 4.65 (d, $J$ = 3.6 Hz, 1H), 4.60 (d, $J$ = 5.6 Hz, 2H), 4.18 (q, $J$ = 4.9 Hz, 1H), 3.88 - 3.82 (m, 1H), 3.77 - 3.67 (m, 2H), 3.66 - 3.60 (m, 1H), 3.51 (t, $J$ = 9.2 Hz, 1H), 3.32 (s, 3H), $^{13}$C NMR (100 MHz, d$_6$-DMSO) $\delta$ 165.6, 160.8, 159.8, 152.9, 146.3, 143.7, 137.7, 136.2, 132.1, 128.8, 128.0, 126.3, 124.4, 120.3, 119.9, 118.4, 116.6, 100.9, 98.5, 81.7, 67.9, 67.5, 62.5, 54.8, 54.4, 51.4, 34.8.

Synthesis of compound 32: To a solution of compound 31 (75 mg, 0.2 mmol, 1.0 equiv) in CH$_3$CN (3 mL) and compound 16 (54.53 mg, 0.24 mmol, 1.2 equiv), CuI (7.6 mg, 0.04 mmol, 02 equiv) and DIEA (0.06 mL, 0.44 mmol, 2.0 equiv) was added and stirred at rt. The reaction was monitored after 7 h at rt to see about 85% conversion. The reaction was further stirred for 22 h total to see full conversion. The crude was further purified by column chromatography using 5% to 50% EtOAc/Hexanes to obtain 79.6% yield (96 mg) of solid white compound as desired product. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.22 (t, $J$ = 5.3, 1H), 1.37 (s, 1H), 1.37 (s, 1H), 7.71-7.64 (m, 2H), 7.43-7.35 (m, 2H), 5.8 (d, $J$ = 9.1, 1H), 5.46-5.37 (m, 2H), 5.25-5.18 (m, 1H), 4.79-4.72 (m, 1H), 4.32-4.24 (m, 1H), 4.16-4.11 (m, 1H), 4.02-3.96 (m, 1H), 2.07 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H),
1.86 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.5, 169.9, 169.3, 168.8, 161.7, 161.2, 154.5, 148.6, 145.4, 134.2, 129.8, 125.3, 120.8, 118.6, 118.2, 116.7, 85.8, 75.2, 72.7, 70.3, 67.7, 61.6, 35.4, 20.7, 20.49, 20.46, 20.1.

**Synthesis of compound 34:** Coumarin-3-carboxylic acid, 14 (200 mg, 1.05 mmol, 1 equiv) was dissolved in 4 mL of anhydrous DCM and stirred in ice-bath for 20 mins. Then oxalyl chloride (0.11 mL, 1.26 mmol, 1.2 equiv) was added followed by one drop of DMF. The mixture was stirred in ice bath for 1 hour and then at rt for 3 h. Mixture was concentrated to obtain the acid chloride derivative as a yellow solid. Compound 33 (100 mg, 0.355 mmol, 1 equiv) was dissolved in 3 mL of anhydrous DCM. The mixture was stirred in ice bath for 20 mins. Pyridine (0.11 mL, 1.42 mmol, 4 equiv) was added and the mixture was again allowed to stir in ice for another 20 mins. The acid chloride formed (90.8 mg, 0.435 mmol, 1.2 equiv) was dissolved in 1.5 mL of anhydrous DCM and was added to the mixture over 30 mins. The mixture was stirred in ice-bath for 1 hour and then at rt for 6 h. LCMS and TLC shows that compound 33 has been completely converted. Mixture was diluted with DCM (15 mL X 2) and washed with 10 mL of water. The combined organic phase was washed with 10 mL sat. ammonium chloride. The crude was dried over sodium sulphate and concentrated under reduced pressure. The product was then purified using flash chromatography on silica gel with a gradient solvent system of Hexanes: DCM: MeOH, and the polarity was increased gradually to optimize the separation. R$_f$ value in 5% MeOH/DCM was 0.70. The product was obtained as a white solid, 128 mg, 79.5% yield, m.p. 211.2-213.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.22 (d, $J = 8.4$ Hz, 1H), 8.90 (s, 1H), 7.68-7.64 (m, 2H), 7.52-7.50 (m, 2H), 7.40-7.35 (m, 5H), 5.59 (s, 1H), 4.83 (d, $J = 3.7$ Hz, 1H, H-1), 4.44 (ddd, $J = 8.0$ Hz, $J = 9.7$ Hz, $J = 12.4$ Hz, 1H, H-2), 4.31 (dd, $J = 4.6$ Hz, $J = 10.0$ Hz, 1H, H-6a), 4.10 (t, $J = 9.6$ Hz, 1H, H-3), 3.89 (ddd, $J = 4.6$ Hz, $J = 9.5$ Hz, $J = 14.0$ Hz, 1H, H-5), 3.80 (t, $J = 10.1$ Hz, 1H, H-6a), 3.66
(t, J = 9.2 Hz, 1H, H-4), 3.47 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 162.8, 161.2, 154.5, 149.0, 137.2, 134.3, 129.9, 129.2, 128.3, 126.4, 125.3, 118.5, 118.0, 116.7, 102.0, 99.0, 82.2, 70.8, 68.9, 62.3, 55.6, 54.7; LC-MS m/z calcd for C$_{24}$H$_{24}$NO$_8$ [M + H]$^+$ 454.1 found 454.2.

**Synthesis of compound 36:** Compound 35 (100 mg, 0.26 mmol, 1.0 equiv) was dissolved in DMF (3.0 mL) along with DIEA (0.07 mL, 0.52 mmol, 1.5 equiv). The reaction mixture was stirred for 15 minutes and 20 (64.8 mg, 0.29 mmol, 1.1 equiv) was added to this solution. Then the reaction mixture was heated to 60 °C and let it run for 2 h. After 2 h the starting peaks changed, monitored by $^1$H NMR. The crude was diluted with EtOAc (20.0 mL) and washed with water (7.0 mL). The water layer was washed further extracted with EtOAc (10 mL X 2). The organic layers were collected and dried over Na$_2$SO$_4$ and filtered. The solvent was removed under pressure and crude was further purified by column eluting with 50% EtOAc/Hexanes to 100% EtOAc to obtain yellowish solid as desired product. Yield: 68% (102 mg). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.54-7.45 (m, 2H), 7.38-7.32 (m, 2H), 7.28 (d, J = 9.1 Hz, 1H), 7.12 (dd, J = 9.1 and 2.8 Hz, 1H), 6.88 (d, J = 2.7 Hz, 1H), 6.48 (s, 1H), 6.06 (d, J = 8.8 Hz, 1H), 5.55 (s, 1H), 5.36-5.20 (m, 2H), 4.72 (d, J = 3.7 Hz, 1H), 4.35-4.19 (m, 2H), 3.93 (t, J = 9.6 Hz, 1H), 3.84 (s, 3H), 3.82-3.74 (m, 2H), 3.59 (t, J = 9.1 Hz, 1H), 3.39 (s, 3H), 2.92-2.76 (m, 2H), 2.69-2.56 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.1, 172.0, 160.7, 156.2, 148.5, 148.0, 137.2, 129.1, 128.2, 126.3, 119.4, 118.3, 117.4, 113.6, 106.3, 101.9, 98.9, 81.9, 70.4, 68.9, 62.5, 61.4, 56.0, 55.3, 54.3, 30.7, 29.3.

**Synthesis of compound 38:** Glutaric acid (200.0 mg, 1.51 mmol, 1.0 equiv) was dissolved in 5.0 mL of thionyl chloride along with a drop of DMF, in nitrogen flushed 50.0 mL RBF and refluxed for 3 h to observe complete consumption of starting material. Excess thionyl chloride was removed under reduced pressure and crude was taken to next step without further purification.
**Synthesis of compound 40:** To a stirring mixture of an ice-cooled solution of dry AlCl₃ powder (605.5 mg, 4.54 mmol, 3.0 equiv) in DCM (6.0 ml), glutaryl chloride (255.8 mg, 0.38 mmol) and 2-chloro-5-methylthiophene (39, 0.35 mL, 3.17 mmol, 2.1 equiv) were successively added dropwise. The reaction mixture was stirred for 3.0 h at room temperature, the color of the reaction mixture turns to dark red. Ice-cold mixture solution of conc. HCl (4.0 mL) and ice (6.0 g) were carefully added to the reaction mixture, and the water layer was extracted with DCM (3 × 10.0 ml). The combined organic phases were washed with saturated aqueous solution of NaHCO₃ (6.0 mL), water (5.0 mL) and NaCl saturated solution (5.0 mL), dried (Na₂SO₄), filtered and the solvent was evaporated in vacuo to yield a brown tar. The crude was further purified by 3% EtOAc/Hexanes to obtain white solid as pure compound. Yield 83.7 % (458.0 mg). ¹H NMR (400 MHz, CDCl₃) δ 7.18 (s, 2H), 2.86 (t, J = 6.9 Hz, 4H), 2.66 (s, 6H), 2.09 – 2.03 (m, 2H).

**Synthesis of compound 41:** A mixture of TiCl₄ (256.552 mg, 1.4 mmol, 2.0 equiv), Zn powder (439.4 mg, 6.72 mmol, 12.0 equiv) and THF (10.0 ml) was stirred under nitrogen at reflux temperature for 1 h. The mixture was cooled to 0 °C, and 40 (200.0 g, 0.56 mmol, 1.0 equiv) was added. The mixture was refluxed for 14 h, to see full conversion. The reaction mixture was then quenched with two drops of saturated aq. K₂CO₃ and passed through celite and washed with EtOAc (20 mL X 3), the combined organic layers was washed with water (20.0 ml) and sat. NaHCO₃(20.0 mL), dried with anhydrous Na₂SO₄ and the solvent was removed in vacuo. Further purification was done by column chromatography (tall column with 100% Hexanes as solvent): Yield: 76% (139 mg). ¹H NMR (400 MHz, CDCl₃) δ 6.57 (s, 2H), 2.71 (t, J = 7.5 Hz, 4H), 2.06 – 1.98 (m, 2H), 1.89 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 134.8, 134.4, 133.3, 126.7, 125.2, 38.3, 22.8.
Procedure for \(n\)-butyl lithium titration\(^{166}\)

\[
\begin{align*}
\text{DPAA} & \quad \xrightarrow{n-\text{BuLi}} \quad \text{Colorless} & \quad \xrightarrow{n-\text{BuLi}} \quad \text{Yellow End Point}
\end{align*}
\]

Diphenylacetic acid (DPAA, 50.0 mg, 0.23 mmol, 1 equiv) added to a dried scintillation vial under \(\text{N}_2\) atmosphere. Anhydrous THF (1.0 mL) was added to the scintillation. 700 \(\mu\)L of 1.6 \(\text{N}\) \(n\)-butyl lithium solution (in hexanes) was added slowly. Each drop temporarily turned the solution yellow and then back to colorless. The \(n\)-butyl lithium solution was added until the solution in the vial turned deep yellow. At the end of the titration, 450 \(\mu\)L of the \(n\)-butyl lithium solution remained in the syringe. The titration required 250 \(\mu\)L of the \(n\)-butyl lithium solution.

\[
\frac{0.235 \, \text{mmole Diphenylacetic acid}}{0.250 \, \text{mL}} = 0.94 \, \text{M}
\]

**Synthesis of compound 42:** Compound 41 (500.0 mg, 1.51 mmol, 1.0 equiv) was dissolved in dry THF (20.0 mL). To this solution \(n\)-BuLi (4.0 mL, 0.94 M in hexanes, ACROS, 2.5 equiv) was added. Yellowish slurry was obtained after addition which was stirred for 1 h. Solid \(\text{CO}_2\) (excess) was added at rt and stirred for 45 min. The reaction was quenched by adding water (10.0 mL), dropwise. The aqueous layer was acidified to \(\text{pH} = 1\) with 2M HCl, extracted with DCM (3 x 25 mL), washed with \(\text{H}_2\text{O}\) (30 mL) organic layers were dried over \(\text{Na}_2\text{SO}_4\), filtered, and concentrated to obtain the brown slurry as crude. Further purification was done by column chromatography (pure hexanes/pure DCM to 2\% \(\text{MeOH}/\text{DCM}\)) to obtain brown solid as desired compound. Yield: 56\% (296 mg). \(^1\)H NMR (400 MHz, \(\text{d}_6\)-DMSO) \(\delta\) 7.40 (s, 2H), 2.77 (t, \(J = 7.5\) Hz, 4H), 2.05 – 1.97 (m, 2H), 1.92 (s, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 162.7, 141.8, 136.5, 134.4, 139.9, 130.5, 37.9, 22.4, 14.4.
Synthesis of compound 43: Compound 42 (100.0 mg, 0.28 mmol, 1.0 equiv) was dissolved in DMF (5.0 mL). To this solution Na₂CO₃ (121.6 mg, 1.14 mmol, 4.0 equiv) was added and let is stir for 30 mins at rt. To this stirring solution, CH₃I (19.6 µL, 0.28 mmol, 1.0 equiv) was added dropwise and let the solution stir for 2.0 h at 40 °C. The reaction was then stopped and DMF was removed under vacuum, diluted with water, and acidified with 2.0 N HCl solution (~pH 2). Extraction was done using DCM (20 mL X 2). Organic layer was washed with H₂O (20 mL) and further dried over anh. Na₂SO₄ and concentrated under reduced pressure. The crude was then purified by using flash chromatography (DCM to 1% MeOH/DCM). Yield: 22% (23 mg, 0.06 mmol, monoester), (27 mg, diester as biproduct, 50% yield based on CH₃I). Rₚ = 0.29 in 5% MeOH/DCM). m.p. 172-174 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.57 (s, 1H), 7.50 (s, 1H), 3.84 (s, 3H), 2.79 (t, J = 7.4 Hz, 4H), 2.08 (m, J = 7.5 Hz, 2H), 1.94 (s, 3H), 1.92 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.5, 162.5, 144.6, 142.7, 137.0, 136.5, 135.9, 135.1, 134.6, 134.4, 129.4, 128.4, 52.0, 38.63, 38.61, 22.8, 14.9, 14.8.

Synthesis of compound 45: To a 50 mL RBF, 42 (75.0 mg, 0.21 mmol, 1.0 equiv) was added along with 3.0 mL SOCl₂ and 2 drops of anh. DMF. The reaction was refluxed for 1.5 h and excess SOCl₂ was removed under vacuum. The acid chloride formed was dissolved in 3.0 mL of anh. DCM and added to the solution of NaSH (72.4 mg, 1.29 mmol, 6.0 equiv) in EtOH (2.0 mL) at 0 °C dropwise over the period of 25 minutes. The resulting solution was stirred for 2.0 h at 0 °C. This solution was quenched with 1M HCl (3.0 mL) and extracted with DCM. The combined organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated to get the thiocarboxylic acid. Then this thiocarboxylic acid was dissolved in EtOH (2.0 mL). A solution of KOH (0.17 mmol) in EtOH (1.0 mL) was added to the thiocarboxylic acid solution. After sonicating this solution for 2 minutes, precipitate was formed, the solvent was removed under
vacuum. The resulting solid was washed with DCM (10.0 mL). The greyish solid was obtained after filtration as desired compound. Yield: 65% (64 mg). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.13 (s, 2H), 2.70 (t, $J = 7.4$ Hz, 4H), 2.00-1.92 (m, 2H), 1.75 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 185.0, 135.5, 133.7, 127.8, 38.2, 22.2, 14.4.

**Synthesis of compound 46**: Compound 41 (200.0 mg, 0.61 mmol, 1.0 equiv) was dissolved in dry THF (7.0 mL) at rt. To this solution $n$-BuLi (1.61 mL, 0.94 M in hexanes, ACROS, 2.5 equiv, 1.51 mmol). Yellowish slurry obtained which was stirred letting it warm up for 1 h. At this point DMF (0.12 mL, 1.51 mmol, 2.5 equiv) was added at rt and stirred for 1 hour. The reaction was quenched by adding the solution to 5.0 mL of aqueous HCl (2N). The mixture was extracted with DCM (3 x 10 mL), organic layers were dried over Na$_2$SO$_4$, filtered and concentrated to obtain the brown slurry as crude. Further purified using column chromatography (pure Hexanes to 7.5% EtOAc/Hexanes). The pure compound was brownish solid 72% (138 mg). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.74 (s, 2H), 7.42 (s, 2H), 2.83 (t, $J = 7.5$ Hz, 4H), 2.17-2.07 (m, 2H), 2.04 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 182.2, 146.3, 140.1, 137.3, 136.9, 134.9, 38.3, 22.8, 15.3.

**Synthesis of compound 47**: To a solution of 46 (138 mg, 0.43 mmol, 1.0 equiv) in methanol (5.0 mL) cooled at 0 °C, NaBH$_4$ (32.99 mg, 0.872 mmol, 2.0 equiv) was added. The reaction was stirred at 0 °C for 2.0 h. The reaction mixture was quenched with saturated solution of NH$_4$Cl (3.0 mL). The methanol was evaporated, and the aqueous phase was extracted with dichloromethane (3 x 10.0 mL). The combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (Hexanes to 50% EtOAc/Hexanes) to obtain oily sample as desired compound. Yield: 79 % (110 mg). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.64 (s, 2H), 4.66 (s, 4H), 2.75 (t, $J = 14.9$ Hz, 4H), 2.07-1.97 (m, 2H),
1.94 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.4, 135.4, 135.1, 134.6, 126.9, 60.1, 38.3, 23.0, 14.3.

**Synthesis of compound 48:** In a 100 mL RBF (oven dried, nitrogen flushed), 47 (freshly prepared and purified, 100.0 mg, 0.31 mmol, 1.0 equiv) was dissolved in DCM (3.0 mL) along with pyridine (0.12 mL, 1.65 mmol, 5.0 equiv). The reaction mixture was stirred at 0 °C for 15 minutes and to this solution tosyl chloride (178.4 mg, 0.93 mmol, 3.0 equiv) dissolved in DCM (2.0 mL) was added dropwise over the period of 20 mins at 0 °C. After complete addition, the solution was allowed to warm to room temperature and was stirred at 0 °C for 4.0 h to see only tosyl peaks but not significant amount of dithienylethenes peaks. The reaction was further stirred at rt for 10 h to see changes in NMR but not significant. The reaction was diluted with DCM (5.0 mL) and washed with NH$_4$Cl followed by water. The organic layers were collected dried under anh. Na$_2$SO$_4$ and concentrated under vacuum to obtain yellowish solid. The color of compound changed to dark brown overnight. $^1$H NMR spectra showed the compound was decomposed. The desired product was not obtained.
CHAPTER 4

PROGRESS ON SYNTHESIS AND CHARACTERIZATION OF ISOXAZOLES BASED SUGAR DERIVATIVES

4.1 INTRODUCTION

Low molecular weight gelators are categorized as the compounds which can form gels in organic solvents, aqueous solvents or mixture of both.\textsuperscript{167,168} The formation of these gels is the result of non-covalent interactions such as hydrogen bonding, hydrophobic interactions and $\pi-\pi$ stacking. Wang lab has been exploring the gelation properties in different sugar-based molecules for more than a decade. Different functional groups such as ether, esters, amides, ureas, N-linked and O-linked carbamates have been utilized to design effective gelators.\textsuperscript{45,169,170} Beside these regular functional groups, a variety of sugar derivatives containing triazoles functional groups performed as good gelators as well. These gels have been characterized and applied for different drug encapsulation and release as well as dye absorption studies, which are applicable in biological sciences as well as environmental clean ups.\textsuperscript{45,171,172}

Some of the isoxazole moiety containing esters have pharmaceutical importance such as being utilized as antibacterial, anticancer and antitumor.\textsuperscript{173-177} Substituted (di- and/or tri-) isoxazoles exhibit wide range of biological activities which are not limited to antibacterial and anticancer, but also analgesic activity,\textsuperscript{178} anti-inflammatory activity,\textsuperscript{179} antioxidant activity,\textsuperscript{180} CNS (central nervous system) activity\textsuperscript{181} and so on.\textsuperscript{182} As shown in Figure 63, compound 1 was evaluated and found to be selective COX-2 inhibitor (IC$_{50}$ 0.95 $\mu$M).\textsuperscript{183} Compound 2 was one of the isoxazole derivative which was screened against four different human cancer cell lines (A549, COLO 205, MDA-MB 231 and PC-3).\textsuperscript{184} It showed the cytotoxic activity against all of them. It
was also confirmed that trifluoromethyl group present in para position of phenyl group of compound 3 promotes the cytotoxicity.\textsuperscript{184} Compound 3 was found to have potential antibacterial activity against \textit{S. aureus} and \textit{A. niger}. when the \textit{p}-position of phenyl ring has chloro or nitro substituent.\textsuperscript{185} The isocarboxazid and isoxazole derivative (Compound 4) was found to be an antidepressant, and it was proved to have unique benefit for the patients who do not respond to any other antidepressants.\textsuperscript{186} Recently Pinheiro’s group synthesized thirty-six isoxazole based C-glycosides of indoles and these glucose, mannose or galactose linked C-glycosides possessed anticancer activity in very low concentration.\textsuperscript{95}

![ Figure 63. Structures of isoxazole based molecules with biological activity. ]

One of the studies of the isoxazole showed that, the alkali ions played a significant role in the formation of the gel when the isoxazole linked esters were hydrolyzed followed by the
interaction with metal ions. A series of isoxazole based low molecular weight gelators and their application for recovery of oil spills have been demonstrated. The isoxazole based gelators were easy to prepare and showed efficient gelation property.

Wang’s lab has been studying the structural and functional properties and their significant changes to their gelation behavior. The peracetylated D-glucosamine (compound 5, Figure 64) and D-glucose (compound 6, Figure 64) based triazoles have been synthesized and their gelation behaviors were tested in different solvents. To understand the change in anomeric position from 5-membered triazole functional group to 5-membered isoxazole, a series of D-glucosamine based aliphatic and aromatic 3,5-disubstituted isoxazole derivatives (compound 6) were synthesized and their gelation behavior was studied. D-glucose based triazoles (compound 7) were also found to be effective gelators. Few analogs for D-glucose based isoxazoles (compound 8) were also synthesized to compare the properties of gels. This study will help us to understand how the change in heteroatoms in aromatic 5-membered ring will affect the gelation behavior of these sugar based low molecular weight gelators.
4.2 RESULTS AND DISCUSSIONS

Aliphatic and aromatic aldehydes (9 a-h) were used to synthesize library of chloroximes (11 a-h) utilizing literature procedure\textsuperscript{187-189} (scheme 1) via oximes (10 a-h) intermediate. These chloroximes were reacted with peracetylated glucosamine with terminal alkyne linked in anomeric (C1) position (compound 12) to obtain isoxazole derivatives. The reaction condition used were mild which includes sodium hydrogen carbonate as base, t-butanol/H\textsubscript{2}O at rt for 4-16 h. To improve the synthetic method, few of the derivatives were synthesized using ethylacetate as solvent. The base helps to form the reactive intermediate nitrile oxide which undergo \[3 + 2\] cycloaddition reaction with sugar based terminal alkyne to give heterocyclic ring named as isoxazoles. These compounds were further purified and characterized before testing their gelation properties. Purification was done by trituration, recrystallization or column chromatography. One of the amides linked isoxazole derivative was also synthesized from C2 position of glucosamine.
(Scheme 3). The terminal alkyne of 14 was reacted with benzenechloroxime to obtain isoxazole, 15. The gelation properties for C1 and C2 based isoxazoles were compared and analyzed.

Different organic solvents, water and mixture of organic solvents and water were used for their gelation test. These results are summarized in Table 1. Most of the compound formed gels at different concentration. There are several organogelators as well as hydrogelators. Both C1 and C2 analogs showed hydrogelation properties. All the compounds showed gelation behavior in glycerol with minimum gelation concentration of 20 mg/mL or lower. While comparing the organic solvent and aqueous solvents, most of these molecules tend to form gel with mixture of water and organic solvents. Compound 13a showed tendency to form gels in every solvent tested except EtOH: H2O, where it precipitated. It formed partial gels in toluene, IPA and EtOH whereas it was very good hydrogelator with MGC of 2.0 mg/mL. From table 1, we can see how different substituents in aromatic ring can impact the gelation behavior of these isoxazole derivatives. This is very noticeable while comparing unsubstituted benzene ring and substituted benzene group. Four out of five substituted benzene in 3-position of isoxazole have formed hydrogel. We can also compare the substituent in 5-position of isoxazole with 3-position being unsubstituted benzene. We found that alkyl spacer between glucosamine (C1 and C2) can also play significant role in the formation of gels. Figure 65 shows the transparent and opaque gels formed by compound 13a in a mixture of two different solvents.
Scheme 12. Synthesis of isoxazole based glucosamine derivatives (C1-position).
Scheme 13. Synthesis of isoxazole based glucosamine (C2-position) and glucose (C1-position) derivatives.
Table 6. Gelation results for isoxazole based carbohydrates.

<table>
<thead>
<tr>
<th>Cpd</th>
<th>Tol</th>
<th>IPA</th>
<th>EtOH</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>
<th>H$_2$O</th>
<th>Glycerol</th>
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<tr>
<td>13a</td>
<td>PG</td>
<td>PG</td>
<td>PG</td>
<td>G10$_o$</td>
<td>P</td>
<td>G6.7$_T$</td>
<td>G10$_o$</td>
<td>G2.0$_T$</td>
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<td>P</td>
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<td>PG</td>
<td>G20$_o$</td>
<td>PG</td>
<td>PG</td>
<td>G20$_T$</td>
<td></td>
</tr>
<tr>
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<td>S</td>
<td>P</td>
<td>S at rt</td>
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G, gel at room temperature; the number in the table are the minimum gelation concentrations in mg/mL; I, insoluble; P, precipitate; UG, unstable gel; S, soluble at 20 mg/mL; UG, unstable gel.
Figure 65. Pictures of gels formed by isoxazole derivatives. (A) compound 13a in EtOH: H₂O (v/v 1:2) at 5.0 mg/mL; (B) compound 13a in H₂O at 2.0 mg/mL.

The gels formed by compound 13a in solvent were evaluated for the absorption of toluidine blue dye. (Figures 66 and 67). First, small glass column was prepared by adding hot solution of 5.0 mg/mL of the compound. Then it was let to cool to form the gel. The toluidine blue solution was then passed through the gel. The UV-vis of the toluidine blue solution before and after passing through the gel column is shown in Figure 66. Calibration curve of the TBO dye solution was used to estimate the amount of toluidine blue absorbed by the gel. We found that about 83% of toluidine blue dye was absorbed. This result is significant to show that the isoxazole based hydrogelator is capable of dye absorption and can be used for environmental remediation.
Figure 66. Gel column for the dye absorption experiment. (A) Gel column before the experiment, (B) Column after loading with 2 mL of 23.9 µM toluidine blue solution, (C) Toluidine blue solution (2.1 mL) collected after passed through the column.

Figure 67. The UV-Vis spectra of 23.9 µM toluidine blue solution (Standard) before the experiment and after the experiment (Expt).
Figure 68. $^1$H NMR and $^{13}$C NMR spectra of compound 13a in CDCl$_3$. 
Figure 69. $^1$H NMR and $^{13}$C NMR spectra of compound 13c in CDCl$_3$. 
Figure 70. HSQC (top) and COSY (bottom) NMR spectra of compound 13a in CDCl$_3$. 
Figure 71. HSQC (top) and COSY (bottom) NMR spectra of compound 13c in CDCl₃.
Figure 72. IR spectra of compound 13a and 13c.
4.3 CONCLUSION

In summary, we have synthesized and characterized series of aromatic and aliphatic linked isoxazole glycoconjugates. The isoxazole series showed interesting behavior towards gelation. Compound 5a was a hydrogelator with MGC 2.0 mg/mL. We found that the different substituent in aromatic group in 3-position of isoxazole is essential to obtain good gelation. While compared to C2 based isoxazole derivatives, we found that substituent in 5-position of isoxazole can play significant role in the formation of gels. The gel formed by compound 13a was effective at removing toluidine blue dye from aqueous solution. Future studies will include the study of applications of the effective LMWGs, especially those hydrogelators for their potential biomedical and environmental applications, possible applications as ligands for catalysis, and the study on the formation of dimeric glycoconjugates to obtain more effective molecular assemblies or gelators.

4.4 EXPERIMENTAL SECTION

General Procedure: All reactions were carried out under normal condition (1 atm pressure, without catalyst unless otherwise mentioned, rt or heated with specified temperature), reagents and solvents were obtained from commercial suppliers from Sigma-Aldrich, VWR, and Fisher and used directly without any purifications. All reactions unless otherwise noted were carried out in oven dried glassware under nitrogen atmosphere. All purification was conducted by flash chromatography using 230-400 mesh silica gel with a gradient of solvent systems. Thin-layer chromatography (TLC) analysis was performed with aluminum backed TLC plates (Sigma-Aldrich) with UV and fluorescence indicator and visualized using UV lamp at 254 nm then stained with PMA solution. $^1$H NMR and proton-decoupled $^{13}$C NMR spectra were obtained with Bruker 400 MHz spectrometers in DMSO-$d_6$ or CDCl$_3$. The chemical shifts were reported using CDCl$_3$/DMSO-$d_6$ as internal standard at 7.26/2.50 ppm and at 77.0/39.5 ppm, respectively. 2D
NMR experiments (HSQC, COSY) were also conducted to assist the compound characterizations. COSY spectra were used for characterizing the sugar protons as they usually appear between 3-5 ppm. Melting point measurements were carried out using a Fisher Jones melting point apparatus. The IR spectra were obtained using a Bruker Platinum ATR (Alpha) FT-IR Spectrometer, the parameters are resolution; 4 cm\(^{-1}\), 64 scans.

**Dye absorption studies:** The preliminary study for dye absorption was done for compound 13a. Compound 13a (5.0 mg/mL in water) was used to make the gel column. 10 mg of compound 13a was dissolved in 2 mL of H\(_2\)O and heated to obtain clear solution. This hot solution was then transferred to the plugged syringe and let it cool. After the gel was formed 2 mL of toluidine blue solution (23.9 \(\mu\)M) was added from the top and eluted. 2.1 mL of collected light blue solution was used to take UV absorbance. The calibration curve for toluidine blue solution was utilized to calculate the concentration of eluted solution.\(^{190}\) The concentration of toluidine blue solution collected after elution was 4.2 \(\mu\)M, and the total amount of TBO in 2.1 mL of solution was 0.0024 mg. The gel column absorbed total of 82.8% of toluidine blue from the solution.

**Synthesis of compound 10a:** To a solution of compound 1a, 3-Nitrobenzaldehyde (500 mg, 3.3 mmol, 1.0 equiv) in EtOH: H\(_2\)O (2:6 mL) was added hydroxylamine hydrochloride (344.8 mg, 4.96 mmol, 1.5 equiv) followed by sodium acetate (678.5 mg, 8.27 mmol, 2.5 equiv). The solution was refluxed for 2 h to see the full conversion. The heating was stopped and slowly allowed to obtain the recrystallized and pure product (340 mg, 62% by recrystallization).\(^{187}\)

**Synthesis of compound 11a:** To a solution of compound 2a (300 mg, 1.80 mmol, 1.0 equiv) in anhydrous (anh.) DMF (2.0 mL) was added NCS (241.13 mg, 1.8 mmol, 1.2 equiv) dissolved in 2.0 mL of anh. DMF dropwise over a period of 1.0 h. Reaction was let stir for 15 h more and monitored by \(^1\)H NMR to see disappearance of starting material. The solvent was
removed under vacuum and diluted with EtOAc (25 mL) followed by water wash (2 X 10 mL). EtOAc layer was then dried over anh. Na₂SO₄, filtered and solvent was removed under vacuum to obtain yellowish solid. This solid was further washed with water to obtain desired compound as white solid (312 mg, 86%).

**Synthesis of compound 10b:** A mixture of 4-methoxybenzaldehyde (500 mg, 3.67 mmol, 1.0 equiv), NH₂OH·HCl (382.79 mg, 5.50 mmol, 1.5 equiv), and NaOAc (758.77 g, 9.25 mmol, 2.5 equiv) in ethanol (3.0 mL) and water (9.0 mL) was placed into a 100 mL round bottomed flask with a reflux condenser. Then the reaction flask was heated to 95 °C and the reaction progress was monitored by ¹H NMR (at 2.0 h point), to see the disappearance of starting material. The reaction was stopped, EtOH was dried under vacuum and DCM was added to the cloudy water solution and compound was extracted using separatory funnel. The organic layer was dried over anhydrous Na₂SO₄, filtered and solvent was removed under vacuum to obtain brownish viscous liquid which was taken directly to next step.

**Synthesis of compound 11b:** To a solution of compound 2b (1.0 g, 6.61 mmol, 1.0 equiv) in anh. DMF (5.0 mL) was added NCS (883.37 mg, 6.61 mmol, 1.0 equiv) dissolved in 5.0 mL of anh. DMF dropwise over a period of 1.0 h. Reaction was let stir for 15 h more and monitored by ¹H NMR to see disappearance of starting material. The solvent was removed under vacuum and diluted with EtOAc (25 mL) followed by water wash (2 X 10 mL). EtOAc layer was then dried over anh. Na₂SO₄, filtered and solvent was removed under vacuum to obtain brownish liquid. This brown liquid was further washed with water to obtain crude compound as yellowish liquid which was further purified by column chromatography (Hexanes to 2% EtOAc/Hexanes) to obtain white fluffy solid as desired product (77% yield, 950 mg).
**Synthesis of compound 10c:** A mixture of 4-bromobenzaldehyde (1.0 g, 5.40 mmol, 1.0 equiv), NH$_2$OH·HCl (563.37 mg, 8.10 mmol, 1.5 equiv), and NaOAc (1.1 g, 13.5 mmol, 2.5 equiv) in ethanol (6.0 mL) and water (12.0 mL) was placed into a 100 mL round bottomed flask with a reflux condenser. Then the reaction flask was heated to 95 °C and the reaction progress was monitored by $^1$H NMR (at 2.0 h point), to see the disappearance of starting material. The reaction was stopped and let it cool slowly to get the crystals. These crystals were filtered and washed with water to obtain the desired product.$^{187}$ (Yield 93%, 1.0 g)

**Synthesis of compound 11c:** To a solution of compound 2c (1.0 g, 4.99 mmol, 1.0 equiv) in anh. DMF (5.0 mL) was added NCS (667.56 mg, 4.99 mmol, 1.0 equiv) dissolved in 5.0 mL of anh. DMF dropwise over a period of 1.0 h. Reaction was let stir for 5.0 h more and monitored by $^1$H NMR to see disappearance of starting material. The solvent was removed under vacuum and diluted with EtOAc (25 mL) followed by water wash (2 X 10 mL). EtOAc layer was then dried over anh. Na$_2$SO$_4$, filtered and solvent was removed under vacuum to obtain yellowish liquid. It was purified by recrystallization in Hexanes (adding 5 drops of EtOAc in 20 mL of Hexanes).$^{187}$ (Yield 84%, 980 mg)

**Synthesis of compound 10d:** A mixture of benzaldehyde (1.0 g, 9.43 mmol, 1.0 equiv), NH$_2$OH·HCl (982.93 mg, 14.14 mmol, 1.5 equiv), and NaOAc (1.93 g, 23.27 mmol, 2.5 equiv) in ethanol (7.5 mL) and water (25 mL) was placed into a 100 mL round bottomed flask with a reflux condenser. Then the reaction flask was heated to 95 °C and the reaction progress was monitored by TLC (at 1 h point). After full conversion, the mixture was cooled to 0 °C diluted with EtOAc (30 mL) and washed with water (5.0 mL X 2). The organic layer was then dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under vacuum to obtain crude product. This crude was directly taken to the next step.$^{188}$
Synthesis of compound 11d: To a solution of compound 2d (1.0 g, 8.25 mmol, 1.0 equiv) in anh. DMF (5.0 mL) was added NCS (1.1 g, 8.25 mmol, 1.0 equiv) dissolved in 5.0 mL of anh. DMF dropwise over a period of 1.0 h. Reaction was let stir for 12.0 h more and monitored by $^1$H NMR to see disappearance of starting material. The solvent was removed under vacuum and diluted with EtOAc (25 mL) followed by water wash (2 X 10 mL). EtOAc layer was then dried over anh. Na$_2$SO$_4$, filtered and solvent was removed under vacuum to obtain yellowish liquid. Further purification was done by column chromatography (Hexanes to 2% EtOAc) to obtain desired compound as yellowish liquid. (Yield; 71%, 915 mg)

Synthesis of compound 10e: A mixture of 4-chlorobenzaldehyde (1.0 g, 7.1 mmol, 1.0 equiv), NH$_2$OH·HCl (741.5 mg, 10.6 mmol, 1.5 equiv), and NaOAc (1.4 g, 17.7 mmol, 2.5 equiv) in ethanol (6.0 mL) and water (12.0 mL) was placed into a 100 mL round bottomed flask with a reflux condenser. Then the reaction flask was heated to 95 °C and the reaction progress was monitored by $^1$H NMR (at 2.0 h point), to see the disappearance of starting material. The reaction was stopped and cooled down to obtain white crystals which was filtered and washed with water to obtain the desired compound. It was taken to next step without further purification.

Synthesis of compound 11e: To a solution of compound 2e (1.0 g, 6.42 mmol, 1.0 equiv) in anh. DMF (3.0 mL) was added NCS (858.3 mg, 6.42 mmol, 1.0 equiv) dissolved in 3.0 mL of anh. DMF dropwise over a period of 1.0 h at rt. Reaction was let stir for 6.0 h more and monitored by $^1$H NMR to see disappearance of starting material. The solvent was removed under vacuum and diluted with DCM (25 mL) followed by water wash (2 X 10 mL). DCM layer was then dried over anh. Na$_2$SO$_4$, filtered and solvent was removed under vacuum to obtain crude. This was further purified by column chromatography (Hexanes to 2% EtOAc/Hexanes) to obtain white solid as desired product. (Yield: 84%, 1.02 g)
**Synthesis of compound 10f:** To a 100 mL RBF, a mixture of valeraldehyde (1.0 g, 11.61 mmol, 1.0 equiv), NH$_2$OH·HCl (1.21 g, 17.41 mmol, 1.5 equiv), and NaOAc (2.38 g, 29.02 mmol, 2.5 equiv) in ethanol (6.0 mL) and water (12.0 mL) was placed into a 100 mL round bottomed flask with a reflux condenser. Then the reaction flask was heated to 95 °C and the reaction progress was monitored by $^1$H NMR (at 2.0 h point), to see the disappearance of starting material. The reaction was stopped, EtOH was dried under vacuum and DCM was added to the cloudy water solution and compound was extracted using separatory funnel. The organic layer was dried over anh. Na$_2$SO$_4$, filtered and solvent was removed under vacuum to obtain white solid. $^1$H NMR shows the presence of both E and Z isomers.$^{189}$

**Synthesis of compound 11f:** To a solution of compound 2f (0.8 g, 7.9 mmol, 1.0 equiv) in anh. DMF (3.0 mL) was added NCS (1.0 g, 7.9 mmol, 1.0 equiv) dissolved in 5.0 mL of anh. DMF dropwise over a period of 1.0 h. Reaction was let stir for 5.0 h more and monitored by $^1$H NMR to see disappearance of starting material. The solvent was removed under vacuum and diluted with EtOAc (25 mL) followed by water wash (2 X 10 mL). EtOAc layer was then dried over anh. Na$_2$SO$_4$, filtered and solvent was removed under vacuum to obtain yellowish liquid as crude. This crude was further purified using column chromatography (Hexanes to 1% EtOAc) to obtain colorless oil as desired compound. 77 % yield (825 mg), Rf = 0.47 (5% EtOAc/Hexanes).$^{189}$

**Synthesis of compound 10h:** To a solution of compound 1h, 4-nitrobenzaldehyde (500 mg, 3.3 mmol, 1.0 equiv) in EtOH: H$_2$O (2:6 mL) was added hydroxylamine hydrochloride (344.8 mg, 4.96 mmol, 1.5 equiv) followed by sodium acetate (678.5 mg, 8.27 mmol, 2.5 equiv). The solution was refluxed for 2 h to see the full conversion. The heating was stopped and slowly allowed to obtain the recrystallized and pure product (480 mg, 88% by recrystallization).$^{187}$
**Synthesis of compound 11h:** To a solution of compound 2h (300 mg, 1.80 mmol, 1.0 equiv) in anh. DMF (2.0 mL) was added NCS (241.13 mg, 1.8 mmol, 1.2 equiv) dissolved in 2.0 mL of anh. DMF dropwise over a period of 1.0 h. Reaction was let stir for 15 h more and monitored by $^1$H NMR to see disappearance of starting material. The solvent was removed under vacuum and diluted with EtOAc (25 mL) followed by water wash (2 X 10 mL). EtOAc layer was then dried over anh. Na$_2$SO$_4$, filtered and solvent was removed under vacuum to obtain yellowish solid. This solid was further washed with water to obtain desired compound as white solid (290 mg, 80%).

**Synthesis of compound 13a:** To a 50 mL RBF, 3-nitro benzaldehyde chloro oxime (78.1 mg, 0.39 mmol, 1.5 equiv) was added along with EtOAc/H$_2$O (v/v 10:1, 5.0 mL). To this solution, NaHCO$_3$ (87.19 mg, 1.03 mmol, 4.0 equiv) and sugar alkyne (12, 100.0 mg, 0.26 mmol, 1.0 equiv) was added and stirred for 8 h to see complete consumption of starting material. The solvent was dried and to the crude H$_2$O (1.0 mL) and hexanes (2.0 mL) was added to obtain the precipitate, followed by filtration to obtain white solid as desired product, Yield 79% (112 mg) R$_f$: 0.22 (3% MeOH/DCM). m. p. 159.0 – 161.0; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.62 (s, 1H), 8.30 (q, $J = 3.3$, 1H), 8.16 (d, $J = 7.7$, 1H), 7.66 (t, $J = 7.9$, 1H), 6.68 (s, 1H), 5.59 (d, $J = 8.2$, 1H), 5.29 (t, $J = 9.9$, 1H), 5.10 (t, $J = 9.5$, 1H), 4.97 (d, $J = 13.7$, 1H), 4.91- 4.76 (m, 2H), 4.27 (q, $J = 5.6$, 1H), 4.18 (q, $J = 4.6$, 1H), 3.95 (q, $J = 8.7$, 1H), 3.81 – 3.70 (m, 1H), 2.09 (s, 3H), 2.06 – 2.00 (m, 6H), 1.94 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.9, 170.6, 170.4, 169.8, 169.3, 160.7, 148.7, 132.5, 130.6, 130.1, 124.7, 121.8, 101.6, 100.3, 72.0, 68.4, 61.9, 61.5, 54.6, 23.3, 20.7, 20.64, 20.58.

**Synthesis of compound 13b:** To a 50 mL RBF, 4-methoxy benzaldehyde chloro oxime (72.2 mg, 0.38 mmol, 1.5 equiv) was added along with EtOAc (5.0 mL). To this solution, NaHCO$_3$ (32.6 mg, 0.38 mmol, 1.5 equiv) and sugar alkyne (12, 100.0 mg, 0.25 mmol, 1.0 equiv) was added and stirred for 3.5 h to see about 2% conversion. To this solution, 0.3 mL of H$_2$O was added, and
reaction was monitored after 2.0 h to see about 75% conversion. The reaction was let go overnight to see the full conversion. The solvent was dried under reduced pressure and the crude was purified using column chromatography (DCM to 3% MeOH/DCM) to obtain yellowish solid which had very small impurity. This was further purified by trituration using 50% EtOAc/Hexanes to obtain white solid as desired product. 70% yield. Rf: 0.32 (4% MeOH/DCM). m. p. 179.0 – 181.0; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.74 – 7.71 (m, 2H), 6.99 – 6.96 (m, 2H), 6.52 (s, 1H), 5.54 (d, $J = 8.9$, 1H), 5.25 (q, $J = 6.6$, 1H), 5.09 (t, $J = 9.6$, 1H), 4.92 (d, $J = 13.7$, 1H), 4.81 - 4.77 (m, 2H), 4.27 (q, $J = 5.7$, 1H), 4.16 (q, $J = 4.9$, 1H), 4.03 – 3.92 (m, 1H), 3.85 (s, 3H), 3.75 – 3.71 (m, 1H), 2.08 (s, 3H), 2.02 (br, s, 6H), 1.91 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.9, 170.7, 170.3, 169.3, 168.3, 162.1, 161.2, 128.2, 121.2, 114.4, 101.6, 100.2, 72.20, 72.16, 68.4, 62.0, 61.5, 55.4, 54.5, 23.3, 20.7, 20.63, 20.59.

**Synthesis of compound 13c:** To a 50 mL RBF, 4-bromo benzaldehyde chloro oxime (91.2 mg, 0.38 mmol, 1.5 equiv) was added along with $t$-BuOH: H$_2$O (5.0 mL). To this solution, NaHCO$_3$ (32.6 mg, 0.38 mmol, 1.5 equiv) and sugar alkyne (12, 100.0 mg, 0.25 mmol, 1.0 equiv) was added and stirred for 16 h to see about 70% conversion. The reaction was let go to 23 h to see about 90% conversion. The solvent was dried under reduced pressure, dissolved in DCM and washed with water. The organic layer was collected and dried to obtain brownish solid which was triturated using 50% EtOAc/Hexanes to obtain white solid which is about 95% pure. Further purification was done by recrystallization in EtOH:H$_2$O (v/v, 5:1) to obtain white solid as desired product. 73% yield. m. p. 194.0 – 196.0; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.66 (d, $J = 8.5$, 2H 7.59 (d, $J = 8.5$, 2H), 6.56 (s, 1H), 5.56 (d, $J = 8.7$, 1H), 5.27 (t, $J = 9.9$, 1H), 5.09 (t, $J = 9.6$, 1H), 4.94 (d, $J = 13.8$, 1H), 4.85 - 4.77 (m, 2H), 4.27 (q, $J = 5.7$, 1H), 4.16 (q, $J = 4.9$, 1H), 3.99 – 3.92 (m, 1H), 3.78 – 3.69 (m, 1H), 2.08 (s, 3H), 2.06 ~1.99 (m, 6H), 1.91 (s, 3H); $^{13}$C NMR (100 MHz,
Synthesis of compound 13d: To a 50 mL RBF, benzaldehyde chloro oxime (60.55 mg, 0.38 mmol, 1.5 equiv) was added along with EtOAc: 
H₂O (4.0:0.5 mL). To this solution, NaHCO₃ (32.6 mg, 0.38 mmol, 1.5 equiv) and sugar alkyne (12, 100.0 mg, 0.26 mmol, 1.0 equiv) was added and stirred for 24 h to see about full conversion. Further purification was done by column chromatography (DCM to 1.0% MeOH/DCM) to obtain white solid as desired product. Rf: 0.17 (3% MeOH/DCM). (Yield; 82%, 108 mg). m. p. 166.0 – 167.0; ¹H NMR (400 MHz, CDCl₃) δ 7.78 – 7.77 (m, 2H), 7.47 – 7.44 (m, 2H), 6.58 (s, 1H), 5.57 (d, J = 8.4, 1H), 5.26 (q, J = 6.6, 1H), 5.09 (t, J = 9.6, 1H), 4.94 (d, J = 13.9, 1H), 4.82- 4.79 (m, 2H), 4.27 (q, J = 5.7, 1H), 4.16 (q, J = 4.9, 1H), 4.00 – 3.93 (m, 1H), 3.76 – 3.72 (m, 1H), 2.08 (s, 3H), 2.02 (br, s, 6H), 1.91 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.9, 170.6, 170.3, 169.0, 161.6, 132.2, 128.3, 127.7, 124.5, 101.5, 100.3, 72.2, 72.1, 68.4, 62.0, 61.5, 54.5, 23.3, 20.7, 20.63, 20.59.

Synthesis of compound 13e: To a 50 mL RBF, 4-chloro benzaldehyde chloro oxime (73.9 mg, 0.38 mmol, 1.5 equiv) was added along with EtOAc: 
H₂O (v/v 5.0:0.5 mL). To this solution, NaHCO₃ (87.2 mg, 1.03 mmol, 4.0 equiv) and sugar alkyne (12, 100.0 mg, 0.25 mmol, 1.0 equiv) was added and stirred for 15 h to see about full conversion. The reaction was stopped, and 6.0 mL of Hexanes was added to the reaction mixture and triturated to obtain white solid as desired product (75%, 105 mg). m. p. 185.0 – 187.0; ¹H NMR (400 MHz, CDCl₃) δ 7.74 – 7.71 (m, 2H), 7.45 – 7.41 (m, 2H), 6.55 (s, 1H), 5.59 (d, J = 8.8 Hz, 1H), 5.27 (q, J = 6.6 Hz, 1H), 5.09 (t, J = 9.6 Hz, 1H), 4.93 (d, J = 13.9 Hz, 1H), 4.83- 4.78 (m, 2H), 4.27 (q, J = 5.7 Hz, 1H), 4.16 (q, J = 4.9 Hz, 1H), 3.99 – 3.92 (m, 1H), 3.76 – 3.72 (m, 1H), 2.08 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.91 (s,
Synthesis of compound 13f: To a 50 mL RBF, valeraldehyde chloro oxime (105.53 mg, 0.77 mmol, 1.5 equiv) was added along with EtOAc: H2O (v/v 5:0.5 mL). To this solution, NaHCO3 (65.39 mg, 0.77 mmol, 1.5 equiv) and sugar alkyne (12, 200.0 mg, 0.51 mmol, 1.0 equiv) was added and stirred for 16 h to see about 90% conversion. This reaction was stirred for another 4.0 h to see no change, at this point, 1.0 equiv of NaHCO3 was added to the reaction mixture and monitored after 4.0 h to see full conversion monitored by 1H NMR. The reaction was stopped, and solvent was dried under vacuum. The crude solid obtained was triturated (5:1 Hexanes/EtOAc) and was washed with 10.0 mL of water to obtain white solid as desired product (91%, 230 mg). m. p. 143.0 – 145.0; 1H NMR (400 MHz, CDCl3) δ 6.09 (s, 1H), 5.50 (d, J = 8.9, 1H), 5.24 (q, J = 6.6 Hz, 1H), 5.08 (t, J = 9.6 Hz, 1H), 4.85 (d, J = 13.7, 1H), 4.76- 4.69 (m, 2H), 4.26 (q, J = 5.7 Hz, 1H), 4.15 (q, J = 4.9 Hz, 1H), 3.98 – 3.91 (m, 1H), 3.74 – 3.69 (m, 1H), 2.65 (t, J = 7.7 Hz, 2H), 2.09 (s, 3H), 2.023 (s, 3H), 2.021 (s, 3H), 1.91 (s, 3H), 1.67 – 1.59 (m, 2H), 1.43 – 1.34 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 170.9, 170.6, 170.3, 169.3, 167.6, 164.2, 103.3, 100.2, 72.2, 72.1, 68.4, 62.0, 61.5, 54.5, 30.3, 25.6, 23.3, 22.2, 20.7, 20.63, 20.58, 13.7.

Synthesis of compound 13g: To a 50 mL RBF, cinnamaldehyde chloro oxime (70.7 mg, 0.38 mmol, 1.5 equiv) was added along with EtOAc: H2O (v/v 5:0.5 mL). To this solution, NaHCO3 (87.2 mg, 1.03 mmol, 3.0 equiv) and sugar alkyne (12, 100.0 mg, 0.25 mmol, 1.0 equiv) was added and stirred for 16 h to see 100% conversion. The compound was further recrystallized in isopropanol to obtain around 95% pure compound. This was further purified by column chromatography (DCM to 1.5% MeOH/DCM) to obtain white solid as desired compound. Yield:
70% (96 mg) Rf: 0.26 (3% MeOH/DCM). m. p. 178.0 – 179.0; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.53 – 7.51 (m, 2H), 7.41 – 7.31 (m, 3H), 7.13 (q, $J$ = 15.3 Hz, 1H), 6.50 (s, 1H), 5.51 (d, $J$ = 8.9 Hz, 1H), 5.26 (q, $J$ = 6.6 Hz, 1H), 5.10 (t, $J$ = 9.6 Hz, 1H), 4.91 (d, $J$ = 13.8 Hz, 1H), 4.80- 4.75 (m, 2H), 4.28 (q, $J$ = 5.7 Hz, 1H), 4.17 (q, $J$ = 4.9 Hz, 1H), 4.00 – 3.93 (m, 1H), 3.76 – 3.71 (m, 1H), 2.10 (s, 3H), 2.033 (s, 3H), 2.030 (s, 3H), 1.93 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.9, 170.7, 170.3, 169.3, 167.9, 161.8, 134.6, 135.7, 129.1, 128.9, 127.0, 115.7, 100.8, 100.3, 72.2, 68.4, 62.0, 61.5, 54.5, 23.3, 20.7, 20.64, 20.59.

**Synthesis of compound 13h:** To a 50 mL RBF, 4-nitro benzaldehyde chloro oxime (78.1 mg, 0.39 mmol, 1.5 equiv) was added along with EtOAc/H$_2$O (v/v 10:1, 5.0 mL). To this solution, NaHCO$_3$ (87.19 mg, 1.03 mmol, 4.0 equiv) and sugar alkyne (12, 100.0 mg, 0.26 mmol, 1.0 equiv) was added and stirred for 8 h to see about full conversion. The solvent was dried under reduced pressure, and further purified by column chromatography (DCM to 0.5% MeOH/DCM) to obtain white solid as desired product. 88 % yield (126 mg), R$_f$ = 0.24 (3% MeOH/DCM). m. p. 199.0 – 201.0; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.35 – 8.31 (m, 2H), 8.01 – 7.97 (m, 2H), 6.67 (s, 1H), 5.48 (d, $J$ = 8.7, 1H), 5.28 (q, $J$ = 6.6, 1H), 5.10 (t, $J$ = 9.6, 1H), 4.98 (d, $J$ = 14.0, 1H), 4.85- 4.82 (m, 2H), 4.27 (q, $J$ = 5.7, 1H), 4.18 (q, $J$ = 4.9, 1H), 3.99 – 3.92 (m, 1H), 3.77 – 3.73 (m, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.94 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.9, 170.6, 170.3, 169.8, 169.3, 160.7, 148.8, 134.8, 127.7, 124.3, 100.7, 100.4, 72.3, 72.0, 68.3, 61.9, 61.5, 54.6, 23.3, 20.7, 20.63, 20.59.

**Synthesis of compound 15:** To a 50 mL RBF, compound 11d (37.5 mg, 0.24 mmol, 1.0 equiv) was taken and TEA (0.33 mL, 0.24 mmol, 1.0 equiv) was added to it along with 3.0 mL of DCM along with compound 6 (90.5 mg, 0.24 mmol, 1.0 equiv). The mixture was then refluxed for 4 h to see consumption of starting material. The reaction was stopped, and DCM was dried under
vacuum. The crude as dissolved with EtOAc (20 mL) and washed with water (5 mL X 2) to obtain yellow liquid as crude. Further purification was done by column chromatography to obtain yellowish solid as desired compound. Yield: 81% (98 mg) Rf: 0.31 (5% MeOH/DCM). m. p. 148.0 – 149.5; 1H NMR (400 MHz, CDCl3) δ 7.82 – 7.77 (m, 2H), 7.51 – 7.47 (m, 2H), 7.46 – 7.42 (m, 3H), 7.38 – 7.34 (m, 3H), 6.35 (s, 1H), 5.97 (d, J = 8.6 Hz, 1H), 5.56 (s, 1H), 4.74 (d, J = 3.8 Hz, 1H), 4.30 – 4.21 (m, 2H), 3.93 (t, J = 9.6 Hz, 1H), 3.80 – 3.74 (m, 2H), 3.59 (t, J = 9.0 Hz, 1H), 3.39 (s, 1H), 2.88 (t, J = 7.3 Hz, 2H), 2.36 (t, J = 7.3 Hz, 2H), 2.14 – 2.10 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 173.2, 173.1, 137.1, 132.0, 129.9, 129.2, 128.9, 128.6, 128.3, 127.3, 126.7, 126.3, 102.0, 99.4, 98.8, 82.0, 70.5, 68.9, 62.4, 55.3, 54.1, 35.2, 25.8, 23.3.

**Synthesis of compound 17:** To a 50 mL RBF, 3-nitro benzaldehyde chloro oxime (77.9 mg, 0.39 mmol, 1.5 equiv) was added along with EtOAc/H2O (v/v 10:1, 5.5 mL). To this solution, NaHCO3 (87.0 mg, 1.03 mmol, 4.0 equiv) and sugar alkyne (8, 100.0 mg, 0.26 mmol, 1.0 equiv) was added and stirred for 8 h to see complete consumption of starting material. The solvent was dried, and the crude was slurried with H2O (1.0 mL) and hexanes (2.0 mL) following by filtration to obtain white solid as desired product, Yield 86% (118 mg) Rf: 0.45 (50% EtOAc/Hexanes). m. p. 164.0 – 165.0; 1H NMR (400 MHz, CDCl3) δ 8.62 (t, J = 1.6 Hz, 1H), 8.30 (dd, J = 8.22 Hz and 1.20 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.66 (t, J = 8.0 Hz, 1H), 6.67 (s, 1H), 5.22 (t, J = 9.4, 1H), 5.14 – 5.04 (m, 2H), 4.96 (d, J = 13.9, 1H), 4.84 (d, J = 13.9, 1H), 4.68 (d, J = 7.8 Hz, 1H), 4.27 (q, J = 5.7 Hz, 1H), 4.18 (q, J = 4.9 Hz, 1H), 3.78 – 3.73 (m, 1H), 2.09 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 170.5, 170.1, 169.5, 169.33, 169.28, 160.6, 148.7, 132.5, 130.5, 130.1, 124.7, 121.8, 101.4, 100.1, 72.6, 72.2, 71.0, 68.2, 61.7, 61.6, 20.7, 20.6, 20.5.
CHAPTER 5
CONCLUSIONS AND FUTURE WORK

5.1 CONCLUSIONS

Glycoconjugates have been utilized in supramolecular chemistry, drug delivery, tissue engineering, water purification, organocatalyst, and much more. They are versatile and flexible for structural modification, which plays a significant role in designing materials with different functionality. This research has utilized N-acetyl-D-glucosamine (NAG) as the main commercially available starting material. Using NAG as the starting material, three different main classes of new compounds have been synthesized for different applications, as discussed in Chapters (2, 3, and 4). Figure 73 shows the use of NAG to synthesize macrocycles, photoresponsive sugar-based compounds, and isoxazole-based sugar derivatives.

Figure 73. Synthesis of macrocycles, photo responsive molecules and isoxazole based derivatives from N-acetyl-D-glucosamine.
In Chapter 2, the design, synthesis, and characterization of NAG-based macrocycles are discussed. We designed macrocycles with different ring sizes with one or two triazole functional groups in the ring. We synthesized two series of triazole containing macrolactones through intramolecular S$_2$N$_2$ reactions. These reactions were done in 10 mM concentrations and didn’t need high dilution, affording 76-90% yields. We found that these macrocycles have the capability of binding different types of ions. The change in chemical shift with the presence of different tetrabutylammonium halides (TBAX) was observed. Figure 74 shows the structures of two representative macrocycles and the binding of chloride ion with the macrocycle DLM28.

![Figure 74. Macrocycles showing binding properties with tetrabutylammonium halides.](image)

We have also found that these macrocycles can be used as ligands for CuAAC reactions. The use of these ligands has shown the rate acceleration of copper-catalyzed click reactions. We also found that macrocycles decorated with two triazole units contribute more to rate acceleration than macrocycles containing one triazole unit. The synthetic methods developed by this research with short steps and high efficiency can be further applied different heterocycle fused sugar-based macrocycles. In addition, these macrocycles can be further studied for the asymmetric catalysis.
In Chapter 3, different coumarin-based sugar derivatives have been synthesized. Coumarins are linked to different monosaccharide derivatives through click reaction, amide formation, and ester formation reactions. We found that several coumarin derivatives show gelation behavior in different solvents like toluene, isopropyl alcohol, and ethanol. They did not form a gel in pure water but formed gels in a mixture of aqueous solvents like ethanol and water and dimethylsulfoxide and water. The fluorescence properties of these compounds were studied. We found that some of these coumarin glycoconjugates showed increased fluorescence intensity compared to their coumarin precursor. Figure 75 shows the structure of a coumarin glycoconjugate, its fluorescence intensity increased 14 times comparing to unattached coumarin. The fluorescent property of these coumarins can be further studied as fluorescent probes in different fields, such as metal detection, monitoring of heavy metal ions for environmental remediation and in biochemical field.

![Coumarin and its glycoconjugate with different fluorescence properties.](image_url)
In Chapter 4, the self-assembling effect of introduction of isoxazole moiety to the tetraacetyl glucosamine derivatives has been studied. These 5-membered heterocyclic moieties have shown contribution of gelation behavior in these glycoconjugates. We found that different substituents on the isoxazole unit can play a significant role in forming gels. Figure 76 shows two of the isoxazole-based glucosamine molecules which can form hydrogels. The hydrogel formed by one of the isoxazole derivative was used for dye absorption. The result shows that the gel was able to absorb 83% of toluidine blue dye. This dye absorbing properties can be further applied for the removal of dyes from a mixture of solvents in the future. Other future studies include the analysis of self-assembling properties and the study of using other sugar derivatives. The design of these isoxazole-based gelators can be utilized for the design of other sugar-based gelators.

Figure 76. Isoxazole based glycoconjugates (C1 and C2 positions).
5.2 FUTURE RESEARCH

We have encountered challenges in the synthesis of macrocycles via lactonization. As the lactone functional group is more labile to bases, we want to synthesize macrocyclic rings with the lactam functional group. Lactam functional group is more stable than lactones. The deprotection of 3 and 4 benzoyl protecting groups can be accomplished by preserving the lactam functional group. This method will also introduce new macrocycles with the amide functional group, which might serve as better binding sites for different ions.


Regarding the responsive photo project, we will continue with synthesizing the aliphatic thiol group at the end of the diarylethene groups since thiol functional group can give a stronger bond in the preparation of quantum dots.
Optimizing the structural property of the coumarin-linked glycoconjugates and obtain photocleavable systems will be another focus. This work will allow us to develop a photocleavable system.

The isoxazole-based gelators will be explored with other carbohydrate derivatives such as glucose and fructose. The structure and gelation properties of the glucosamine derivatives can help design other sugar-based gelators that contain heterocycle functional groups. Future studies will include the study of applications of the effective LMWGs, especially those hydrogelators for their potential biomedical and environmental applications, possible applications as ligands for catalysis, and the study on the formation of dimeric glycoconjugates to obtain more effective gelators. Further structural optimization of some of these derivatives will be carried out in search of better molecular assemblies.
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APPENDIX A

LIST OF SCHEMES

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Synthesis of mono-triazole sugar linked macrocycles</td>
<td>36</td>
</tr>
<tr>
<td>2. Synthesis of bis-triazole linked sugar-based macrocycles</td>
<td>37</td>
</tr>
<tr>
<td>3. Macro lactonization using other sulfonates as leaving groups</td>
<td>38</td>
</tr>
<tr>
<td>4. Macrolactonization from C2-position</td>
<td>41</td>
</tr>
<tr>
<td>5. Coumarin linked sugar derivatives synthesized by $S_{N}²$ reaction</td>
<td>99</td>
</tr>
<tr>
<td>6. Coumarin linked sugar derivatives synthesized by click reactions, C2 position</td>
<td>100</td>
</tr>
<tr>
<td>7. Synthesis of anomeric triazoles containing coumarin glycoconjugates</td>
<td>100</td>
</tr>
<tr>
<td>8. Synthesis of amide and ester derivatives with different coumarin intermediates</td>
<td>101</td>
</tr>
<tr>
<td>9. Synthesis of photochromic molecules</td>
<td>108</td>
</tr>
<tr>
<td>10. Synthesis of thiol based photochromic molecules</td>
<td>109</td>
</tr>
<tr>
<td>11. Synthesis of chloroximes intermediate</td>
<td>135</td>
</tr>
<tr>
<td>12. Synthesis of isoxazole based glucosamine derivatives (C1-position)</td>
<td>136</td>
</tr>
<tr>
<td>13. Synthesis of isoxazole based glucosamine (C2-position) and glucose (C1-position) derivatives</td>
<td>137</td>
</tr>
<tr>
<td>14. Synthesis of macrolactam</td>
<td>161</td>
</tr>
</tbody>
</table>
APPENDIX B

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Permission for Chapter 1 with schematic representation of different structures for gel, dye release by photoresponsive hydrogel and fluorescent spectra of coumarin glycoconjugates, published by Elsevier, Applied Materials and Organic Letters respectively.
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List of Publications: