ENGINEERED CARBOHYDRATE-BASED MATERIALS FOR BIOMEDICAL APPLICATIONS
Polymers, Surfaces, Dendrimers, Nanoparticles, and Hydrogels

Edited by
RAVIN NARAIN
University of Alberta
Edmonton, Alberta, Canada
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Carbohydrates are the most abundant, easily accessible and cheap biomolecules in nature. Besides their potential uses as key chemical raw materials and energy production, they have been recognized to play a key role in a wide variety of complex biological processes. They are involved to a large extent in mediating recognition processes through their interactions with proteins and other biological entities. They have been recognized to play a significant role in many important cellular recognition processes including cell growth regulation, differentiation, adhesion, cancer cell metastasis, cellular trafficking, inflammation by bacteria and viruses, and immune response. Individual carbohydrate–protein interactions are generally weak, and multivalent forms of carbohydrate ligands are usually involved in those biological processes.

This book has been conceived in order to provide an up-to-date account of the major developments on the biomedical applications of synthetic carbohydrate-based materials. This book is organized into five main themes such as polymers, nanoparticles, surfaces, dendrimers, and hydrogels.

Synthetic glycopolymers are essential macromolecules that display many structural and functional features. With functions similar to those of natural carbohydrates, synthetic glycopolymers with specific pendant saccharide moieties can play a significant role in pathological and biological processes via multivalent carbohydrate–protein interactions. With recent progress in organic and polymer chemistry, functional glycopolymers have been prepared with remarkable ease. Carbohydrate-based polymers with different properties were also synthesized, including biodegradable, thermosensitive, and acid-degradable core-crosslinked glyconanoparticles, with neuroactivity and with chiroptical properties. Chapter 1 provides a comprehensive review on the synthesis of glycomonomers and their corresponding glycopolymers via a wide range of organic and polymerization synthesis approach. Some biological
interaction studies and applications of glycopolymers, such as in antivirus/bacteria and gene delivery, are also described. Chapter 2 discusses the solution properties of block glycopolymers and their biological relevance. The synthesis of smart block glycopolymers using various polymerization techniques has been discussed. The usage of these smart glycopolymers in tissue engineering, drug delivery, and pathogen interactions is discussed. One of the well-studied types of block glycopolymers is cationic glycopolymers. The use of cationic polymers for gene delivery purposes is a facile technique that is extensively studied as a possible source of noninvasive and efficient gene delivery. Chapter 3 discusses the role and importance of cationic glycopolymers for gene delivery purposes. The brief overview of synthesis of cationic glycopolymers by different polymerization techniques is provided. The detailed study of cationic glycopolymer for gene delivery purposes is specifically discussed.

The incorporation of glycopolymers or their corresponding copolymers to macromolecules of choice can further enhance their physiological impact for biological applications. The major challenge in this regard is the synthesis of glycopolymers bioconjugates of controlled dimensions to explore their uses for biomedical applications. Chapter 4 describes the synthetic techniques used in the literature for the production glycopolymers bioconjugates and their importance in biological applications. The facile approaches to synthesize glycopolymers bioconjugates of controlled dimensions are highlighted and their role in biological assays, diagnostics, and in the study of carbohydrate- and protein-based interactions is elaborated.

The synthesis of glycoclusters is an important aspect of synthetic carbohydrate-based materials under study to understand their interactions with macromolecules such as pathogens and several proteins. These interactions of glycoclusters with living organisms or macromolecules make the basics of most biological phenomena, including invasion, metastasis, and infections. Nanotechnology is a rapidly growing field of materials science that has also extensively been explored in biological applications, owing to the facile introduction of functional groups on the surface of nanomaterials. The introduction of glycopolymers-based moieties on the surface of nanomaterials are found to produce glycoclusters with enhanced biological significance compared to glycopolymers alone, due to the multivalent effect of functional groups present on the surface of nanomaterials. These nanomaterials are largely studied in literature as a function of their structure, nature of materials, surface functionalization properties, and morphology-dependent interactions with living organisms. Chapter 5 discusses the various strategies to synthesize glycopolymers-functionalized carbon nanotubes and their interactions in vitro and in vivo. The inherent properties of carbon nanotubes toward cellular uptake and their toxicity issues are discussed. Moreover, the uses of glycopolymers-functionalized nanotubes for biomedical applications, including gene and drug delivery, and tissue engineering is described. Chapter 6 provides a brief overview about the synthesis and surface functionalization of another type of nanomaterial, namely metallic nanoparticles. The synthesis and surface functionalization of gold and magnetic nanoparticles and of quantum dots with biocompatible carbohydrate-based polymers has opened various possibilities for their uses in biotechnology and biomedicines. This chapter describes a review of few biomedical applications of these glyconanoparticles, including their use in pathogen
inhibition, fluorescent probes, magnetic resonance imaging, and cancer metastasis. Another approach to obtain multivalency and to enhance the function of glycopoly-
mers is the synthesis of glycodendrimers, which compared to their corresponding polymers are of controlled molecular weight and architecture. Chapter 7 describes the synthesis of glycodendrimers using various strategies and their interactions with proteins are studied. The interactions of glycodendrimers with various proteins at physiological and pathological levels are the discussed.

In addition to the surface functionalization of nanoscaffolds in colloidal form, the synthesis of glycopolymer-coated macroscaffolds are found to be an attractive platform for the tissue engineering purposes. These glycopolymer-modified surfaces provide not only biocompatibility but are also shown to possess the potential to provide the selectivity in cellular growth and proliferation. Chapter 8 provides a detailed overview of the synthetic techniques involved in the functionalization of macroscaffolds with glycopolymers or their corresponding copolymers. Moreover, the characterization of these surfaces and their role in tissue engineering and as nonfouling surfaces for the inhibition of pathogens is discussed. Chapter 9 provides a different synthetic route to produce biomaterials for tissue engineering and gene delivery. The chapter focuses on the synthesis of glycopolymer-functionalized hydrogels by various techniques. The use of these hydrogels in tissue engineering and drug delivery is discussed. Chapter 10 mainly focuses on the modification of natural carbohydrate-based scaffolds for drug delivery purposes via various administration routes. These modifications are thought to increase the efficacy of drug delivery, in addition to eliminating the hypersensitivity reactions associated with various drug treatments.

Ravin Narain
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CHAPTER 1

SYNTHESIS OF GLYCOPOLYMERS

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SYNTHESIS OF GLYCOPOYMERS

1.1 INTRODUCTION

Glycopolymers—synthetic polymers with pendant carbohydrates—have received considerable attention in the fields of polymer chemistry, material science, and biomedicine due to their biocompatibility and their bioactivity. From humble beginnings where glycopolymers were synthesized from vinyl-functionalized sugars via free radical polymerization with little control over the resulting polymer characteristics, glycopolymer synthesis has now developed into a mature area where the control over molecular weight and polymer architecture is routinely sought and indeed achieved. Glycopolymers synthesis has now infiltrated most known techniques of polymer synthesis and is not restricted to controlled radical processes; ionic techniques also provide feasible means to polymerize glycomonomers in a controlled manner.

The aim of this chapter is to provide a comprehensive review of all the techniques that have been utilized for the synthesis of glycopolymers; however, greater emphasis will be placed on the techniques that supercede free radical polymerization. After highlighting the important achievements in the synthesis of glycopolymers via free radical polymerization, focus will turn toward glycopolymer synthesis via the controlled/living radical polymerization processes known as nitroxide-mediated polymerization (NMP), cyanoxyl-mediated polymerization, atom transfer radical polymerization (ATRP), and reversible addition–fragmentation chain transfer (RAFT) polymerization. Glycopolymers synthesis by ring-opening polymerization (ROP), anionic polymerization and cationic polymerization will detail the progress made in the area of ionic polymerization, and a discussion of the work carried out using ring-opening metathesis polymerization (ROMP) will conclude the section on the synthesis of glycopolymers by polymerizing sugar-containing monomers. The functionalization of reactive polymer scaffolds with carbohydrate species will then be discussed as an alternative strategy for synthesizing glycopolymers.

1.2 SYNTHESIS OF VINYL-CONTAINING GLYCOMONOMERS

1.2.1 Monomers from Protected Carbohydrates

The commercial availability of a range of carbohydrates provides access to a wide array of different glycomonomers, and significant efforts have been dedicated to the synthesis of polymerizable vinyl sugars. In an early feature article, Wulff et al. [1] highlighted possible avenues for generating glycomonomers in which an important distinction must be made between protected and unprotected carbohydrates. The choice of employing protected or unprotected sugars is dependent on the ease of stereospecific functionalization of the sugar, the solubility of the monomer and polymer, the potential incompleteness of the removal of the protective group, and the ease of purification. The most common synthetic approaches are outlined below, but they are discussed in more detail elsewhere [1].
1.2.1.1 Reactions Using Isopropylidene-Protected Sugars  Many sugars can easily be protected using acetone to form isopropylidene derivatives. This approach, which is suitable for a range of sugars including glucose, galactose, fructose, and sorbose, allows easy functionalization of the remaining hydroxyl functionality with acrylate [2], methacrylate [3], and 4-vinylbenzyl groups [4].

1.2.1.2 Glycosides from Halogeno Sugars  Glycoside monomer synthesis via the reaction between halogeno sugars and hydroxyl groups of vinyl-containing species has been explored in detail with varying degrees of success. The starting materials, typically acetylated 1-halogeno sugars, can be expensive or difficult to obtain, but the technique is especially useful for inserting longer spacers between the polymerizable moiety and the sugar. The cleavage of the acetyl protecting groups in alkaline media does not affect the glycoside bond [5].

1.2.1.3 Grignard Reactions  The aldehyde functionality of a sugar molecule can be targeted by Grignard reagents [6]. Prior protection of the remaining hydroxyl groups is essential.
SYNTHESIS OF GLYCOPOLYMERS

1.2.2 Monomers from Unprotected Sugars

1.2.2.1 Enzymatic Trans-esterification Enzyme-catalysed trans-esterification reactions present a highly efficient and regioselective avenue for obtaining glycomonomers that would otherwise be inaccessible without utilizing protecting groups. The reaction of sugars with vinyl-containing esters in organic solvents is catalyzed by lipases such as Candida antarctica, usually yielding derivatives functionalized in 6-position [7], although efficient functionalization in the 1-position has also been reported [8].

1.2.2.2 Fischer Glycoside Synthesis Direct monosubstitution in the anomeric (C-1) position without the recourse to protective chemistry can be achieved by the reaction of an excess of hydroxyl groups, such as in hydroxyethyl acrylate, with the sugar in the presence of phosphomolybdic acid as catalyst [9].

1.2.2.3 Synthesis via Barbituratic Acid Barbituratic acid reacts readily with the C-1 position of the unprotected sugar to generate a reactive salt. Subsequent reaction with bromides such as 4-vinyl benzyl bromide leads to polymerizable monomers. Conversion of the barbituratic acid ring to a diamide further improves water solubility [10].

1.2.2.4 Conversion of Aminosugars A popular route to glycomonomers is the fast reaction between aminosugars and acyl halides or anhydrides. The high reactivity of the amine group ensures its preferential reaction even in the presence of unprotected hydroxyl groups. Reactions of acryloyl chloride and methacryloyl
chloride [11] and also isocyanates [12] and epoxides with various aminosugars have been explored to confer the glycomonomers in high yields.

1.2.2.5 Reaction between Oxidized Sugars and Amines

A range of amide-linked glycomonomers are accessible from sugars that have been oxidized to their corresponding lactones and can therefore be reacted with vinyl-functionalized amines [13].

While these are the most common strategies used for glycomonomer synthesis, other pathways have emerged in recent years such as Cu(I) click chemistry [14]. Some of these approaches are highlighted in this chapter.

1.3 CONVENTIONAL FREE RADICAL POLYMERIZATION

Free radical polymerization is one of the most widely used techniques for making polymers. The polymerization reaction is initiated by free radical initiators and has been used to synthesize linear vinyl saccharide polymers since the 1960s. Despite its disadvantages, such as high polydispersities of the resulting polymers and difficulties in controlling terminal functionalities, the robustness of free radical polymerization has encouraged its widespread use. Indeed, a large number of reports have emerged on the synthesis of glycopolymers via free radical polymerization in both aqueous and nonaqueous media.

Glycopolymers, polymers with pendant sugar groups, were first reported in 1961 when Kimura et al. [15] and Whistler et al. [11a, 11c] reported the free radical homo- and copolymerization of glycomonomers. Significant activity in the field of free radical polymerization of glycomonomers emerged in the following years, which only declined in the late 1990s with the birth of living free radical polymerization.
SYNTHESIS OF GLYCOPOLYMERS

techniques. The feature article by Wulff et al. [1] highlighted the body of work and the array of structures. Here, we only highlight some of the latest achievements in this area, mainly publications after 1990.

1.3.1 Acrylamide Monomers

Roy et al. copolymerized 4-acrylamidophenyl-β-lactoside (Table 1.1, entry 1) and acrylamide in water at 90°C in the presence of ammonium persulfate (APS) and tetramethylethylenediamine (TMEDA) [16]. The antigenicity of the resulting carbohydrate copolymer was then demonstrated by agar gel diffusion with peanut and castor bean lectins. Nishimura et al. outlined the synthesis of 3-(N-acryloylamino)propyl 2-acetamido-2-deoxy-β-D-glucopyranoside [17] (Table 1.1, entry 2) and 3-(N-acryloylamino)propyl O-(β-D-galactopyranosyl)-(1-4)-2-acetamido-2-deoxy-β-D-glucopyranoside [18] (Table 1.1, entry 3) and polymerized them in a similar manner to Roy et al. [16].

Methacrylamide-functionalized mannose monomers (Table 1.1, entries 4–5) were polymerized by Tagawa et al. using a lipophilic azo-initiator containing two long alkyl chains per initiating fragment [19]. Incorporation of the amphiphiles into liposomes generated structures that were able to recognize Concanavalin A (Con A) with little difference observed between the species with varying spacer lengths between the polymer backbone and the sugar residue. Also starting with protected sugars, Carpino et al. reported the synthesis of 2,3,4,6-tetra-O-acetyl-1-OS-(4-methacryloylaminophenyl)-β-D-glucopyranoside (Table 1.1, entry 6) and 1-OS-(4-methacryloylaminophenyl)-β-D-glucopyranoside (Table 1.1, entry 7), and homopolymerized them with 2,2′-azobisisobutyronitrile (AIBN) as initiator in dimethylformamide (DMF) to afford polymers that were then deprotected with sodium methoxide to give water-soluble glycopolymers [20].

1.3.2 (Meth)acrylate Monomers

Novel (meth)acrylic monomers (Table 1.1, entry 9) bearing a monosaccharide residue were developed by Kitazawa et al. by reacting methyl glycosides with 2-hydroxyethyl acrylate or methacrylate in the presence of heteropoly acid. The monomers were then polymerized in aqueous solution with potassium persulfate as initiator [9].

A galactose-based monomer containing a galactopyranose unit attached through an ester linkage to a vinyl group (Table 1.1, entry 10) was synthesized by Fortes and co-workers and was then copolymerized with ethyl acrylate in DMF under free radical conditions [22].

The protected monomers 2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucosyloxy)ethyl methacrylate (Table 1.1, entry 11) and 2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactosyloxy)ethyl methacrylate (Table 1.1, entry 12) were polymerized by Cameron et al. in chloroform, and the polymers deacetylated in a mixture of dichloromethane and methanol [23]. The alternative approach for obtaining deprotected polymers was also adopted; entries 11 and 12 were deprotected to give the corresponding monomers 2-(β-D-glucosyloxy)ethyl methacrylate (GlcEMA; Table 1.1, entry 13) and
<table>
<thead>
<tr>
<th>Carbohydrate</th>
<th>Entry</th>
<th>Monomer</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Initiator</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>1</td>
<td></td>
<td>H₂O</td>
<td>0°C</td>
<td>APS</td>
<td>16</td>
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<tr>
<td>Glucosamine</td>
<td>2</td>
<td></td>
<td>H₂O</td>
<td>25°C</td>
<td>APS</td>
<td>17</td>
</tr>
<tr>
<td>Lactosamine</td>
<td>3</td>
<td></td>
<td>H₂O/DMsO</td>
<td>50°C</td>
<td>APS</td>
<td>18</td>
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<tr>
<td>Mannose</td>
<td>4</td>
<td></td>
<td>2:1 THF/MeOH</td>
<td>70°C</td>
<td>DODA-ACPA</td>
<td>19</td>
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(continued)
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<th>Monomer</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Initiator</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Mannose</td>
<td>5</td>
<td>( n = 4; \text{H}_2\text{O} ) ( n = 7; 1:1 \text{THF/MeOH} )</td>
<td>( 70^\circ \text{C} )</td>
<td>V50 DODA-ACP</td>
<td>19</td>
</tr>
<tr>
<td>Glucose</td>
<td>6</td>
<td>DMF</td>
<td>60°C</td>
<td>AIBN</td>
<td>20</td>
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<tr>
<td>Glucose</td>
<td>7</td>
<td>DMF</td>
<td>60°C</td>
<td>AIBN</td>
<td>20</td>
</tr>
<tr>
<td>Reagent</td>
<td>Temp</td>
<td>Solvent</td>
<td>Added Compounds</td>
<td>Notes</td>
<td></td>
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<td>------</td>
<td>---------</td>
<td>-----------------</td>
<td>------------------------------</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>40°C</td>
<td>Benzene</td>
<td>Glucose, Galactose, Mannose, Xylose</td>
<td>No mention KPS in paper</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80°C</td>
<td>DMF</td>
<td>Glucose</td>
<td>AIBN</td>
<td></td>
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<tr>
<td>H₂O</td>
<td>65°C</td>
<td>Chloroform</td>
<td>G. glucoside or galactoside or xyloside</td>
<td>No mention in paper</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>R = CH₃ or H</td>
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(continued)
### TABLE 1.1 Glycomonomers Synthesized via Free Radical Polymerization (Continued)

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<th>Entry</th>
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<th>Temperature</th>
<th>Initiator</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Glucose</td>
<td>12</td>
<td>AcO</td>
<td>Chloroform</td>
<td>65°C</td>
<td>AIBN</td>
<td>23a, 23b</td>
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<td>H2O/MeOH</td>
<td>65°C</td>
<td>K2S2O8</td>
<td>23a</td>
</tr>
<tr>
<td>Glucose</td>
<td>14</td>
<td>OH</td>
<td>H2O/MeOH</td>
<td>65°C</td>
<td>K2S2O8</td>
<td>23a, 23b</td>
</tr>
<tr>
<td>Glucose</td>
<td>15</td>
<td>OAc</td>
<td>Chlorobenzene</td>
<td>70°C</td>
<td>AIBN</td>
<td>24</td>
</tr>
<tr>
<td>Galactose</td>
<td>16</td>
<td>AcO</td>
<td>Chlorobenzene</td>
<td>70°C</td>
<td>AIBN</td>
<td>24</td>
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</table>

1. For entries 12 and 13, the monomer is AcO. For entry 14, the monomer is HO. For entry 15, the monomer is OAc. For entry 16, the monomer is CO2Et.
Arabinose 17

Fructose 18

Galactose 19

70 °C AAPD, AIBN 25, 26

H₂O, DMF
<table>
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<tr>
<th>Carbohydrate</th>
<th>Entry</th>
<th>Monomer</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Initiator</th>
<th>Reference</th>
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<td>Lactose</td>
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<td>RT</td>
<td>KPS</td>
<td>27</td>
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<tr>
<td>Lactose</td>
<td>21</td>
<td>Lactose</td>
<td>H₂O</td>
<td>25°C</td>
<td>KPS</td>
<td>28</td>
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<tr>
<td>Maltose</td>
<td>22</td>
<td>Maltose</td>
<td>DMSO, H₂O</td>
<td>60°C</td>
<td>AIBN, KPS</td>
<td>13b, 30</td>
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Lactose 23
DMSO, H2O, 60°C, AIBN, KPS 13h, 30

Maltotriose 24
DMSO, H2O, 60°C, AIBN, KPS

Lactose 25
DMSO, 60°C, AIBN

Lactosamine 26
DMSO, 60°C, AIBN

(continued)
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<th>Carbohydrate</th>
<th>Entry</th>
<th>Monomer</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Initiator</th>
<th>Reference</th>
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<td>Glucose</td>
<td>27</td>
<td><img src="image" alt="Glucose Monomer" /></td>
<td>DMSO</td>
<td>60°C</td>
<td>AIBN</td>
<td>30</td>
</tr>
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<td>Glucuronamide</td>
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<td>DMSO</td>
<td>60°C</td>
<td>AIBN</td>
<td>30</td>
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<tr>
<td>Galactose/gluconamide</td>
<td>29</td>
<td><img src="image" alt="Galactose/Gluconamide Monomer" /></td>
<td>DMSO</td>
<td>60°C</td>
<td>AIBN</td>
<td>30</td>
</tr>
</tbody>
</table>
$\alpha,\alpha'$-Galactotrehalose

$\alpha,\beta'$-Galactotrehalose

Glucosamine

$DMSO, H_2O$

$60^\circ C$

$AAPD$

$H_2O$

RT

APS

$n = 1 \text{ or } 2 \text{ or } 3 \text{ or } 9$

(continued)
TABLE 1.1 Glycomonomers Synthesized via Free Radical Polymerization (Continued)

<table>
<thead>
<tr>
<th>Carbohydrate</th>
<th>Entry</th>
<th>Monomer</th>
<th>Solvent&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Temperature</th>
<th>Initiator&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactosamine</td>
<td>33</td>
<td><img src="image1" alt="Lactosamine Structure" /></td>
<td>H₂O</td>
<td>RT</td>
<td>APS</td>
<td>32</td>
</tr>
<tr>
<td>Chitobiose</td>
<td>34</td>
<td><img src="image2" alt="Chitobiose Structure" /></td>
<td>H₂O</td>
<td>RT</td>
<td>APS</td>
<td>32</td>
</tr>
<tr>
<td>Lactosamine</td>
<td>35</td>
<td><img src="image3" alt="Lactosamine Structure" /></td>
<td>H₂O</td>
<td>RT</td>
<td>APS</td>
<td>33</td>
</tr>
<tr>
<td>Galactose</td>
<td>36</td>
<td><img src="image4" alt="Galactose Structure" /></td>
<td>Copolymerization in different solvents</td>
<td>65°C</td>
<td>AIBN</td>
<td>34</td>
</tr>
</tbody>
</table>