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New Glucosamine Derivatives Based Reducing Disaccharides via Schiff Reaction

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Abstract

Due to the importance of glucosamine, this project aims to improve its role in medicinal and pharmaceutical applications and find new derivatives derived from glucosamine with useful and beneficial applications. We planned to couple two important glucosamine compounds, 6-deoxy-6-amino-D-glucose and 2-deoxy-2-amino-D-glucose, with two reducing disaccharides (D-lactose and D-maltose) via Schiff coupling because the two compounds, glucosamine and reducing disaccharides, have the required function groups for the Schiff reaction: the amine groups and the aldehyde groups. The synthesis and physical properties of a series of four compounds [1–4] were performed and subjected to spectroscopic characterization by ^{1}H and ^{13}C NMR to prove their correct structures and full purity. The biological activity was tested for two compounds [1 and 2] only due to a shortage of funding; compound [**1**] shows excellent activity toward two kinds of gram-negative and gram-positive bacteria, which are resistant to penicillin, while compound [**2**] doesn't show any activity against this kind of bacteria.

Keywords: Schiff reaction, reducing disaccharides, anomeric center, enantiomers, asymmetric carbon.

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Introduction

Glucose amine (6-deoxy-6-amino-D-glucose and 2-deoxy-2-amino-D-glucose) is a useful compound in medical and pharmaceutical applications[1, 2]. Glucosamine's chondroprotective qualities and long-term effects make it one of the most widely utilized substitutes in the world. Its application to the management of osteoarthritis is well-established[3]. Their availability, biodegradability, and reasonable prices make them candidate compounds for developments or modifications to another compound with new advantages. The chemical structure of those compounds containing both carbonyl and hydroxyl groups and an amino group makes scientists and researchers think about coupling them with other compounds to produce new ones. Many modifications are reported via different chemical classes of compounds.

Beata Liberek *et al.* reported the synthesis of some N-alkyl derivatives of 2-amino-2-deoxy-d-glucose as antifungal activity[4] . Tatiana V and co-authors synthesized 1-BODIPY-labeled 2-amino-2-deoxy-d-glucose as a new fluorescent substrate for acetyl-CoA [5]. Jian Yang and his co-author review the stereoselective formation of 1,2-cis-aminoglycosides as a biological active agent [6, 7]. Some 2-deoxy-2-fluro-D-glucose derivatives were reported for clinical and animal radiotracer studies[8] . Some of the 2-deoxy-2-amino-D-glucose molecules are announced as anticancer agents [8-13] . Methyl 6-aminodeoxy-d-pyranoside-derived platinum (II) glycoconjugate synthesis was reported, tested, and shown to have an antitumor effect[14]. Schiff base metal complexes were successfully synthesized by combining 1,2-phenylenediamine and 2-aminophenol with D-glucose and Co(II), Ni(II), and Cu(II) [15]. A new series of compounds were synthesized by coupling. 1,1,2-trimethyl-1H-benzo[e]indole with 2-deoxy-2-amino-d-glucose and 6-deoxy-6-amino-d-glucose as potentially bioactive compounds[16]. The reaction of terephthalaldehyde with d-glucosamine via the Schiff reaction produced new modified molecules with optical properties and high bacteriostatic activity that make them useful as fluorescent probes for tumor cell imaging[17]. 6-amino-6-deoxy-glycoglycerolipids derived from 2-O-β-d-glucopyranosylglycerol were synthesized and reported to have anti-tumor-promoting activity [18]. Glucosamine is more effective than a placebo at reducing pain in knee osteoarthritis patients in long-term treatment[19]. Some sugar derivatives of 2-acetamido-2-

deoxy-d-glucose-based amino acids were synthesized and reported as building blocks for the design and synthesis of natural glycoconjugates mimetics[20].

Accordingly, our aim is to find improved new moleculesby coupling glucosamine with disaccharides. The reducing disaccharides are soluble in water due to the presence of enough hydroxyl groups and the presence of free aldehyde groups, which makes the coupling with glucosamine easy through Schiff coupling. Therefore, two disaccharides were chosen (D-lactose and D-maltose) for coupling with (6-deoxy-6-amino-D-glucose and 2-deoxy-2-amino-D-glucose) via the Schiff reaction to find new carbohydrates with imine linkages.

Materials and Methods

General Procedures of Schiff Reaction

At room temperature, a solution of reducing disaccharides (D-lactose or D-maltose) (1 eq.) in 10–15 mL CH_3CH_2OH was combined with glucosamine (2-deoxy-2-amino-d-glucose or 6-deoxy-6-amino-D-glucose) (1 eq.) in 20–25 mL ethyl alcohol. After adding around ten drops of acetic acid, the mixture was refluxed for roughly fifteen hours progressively. Thin Layer Chromatography (TLC): n-hexane: ethyl acetate ratio of 4:1 was employed, indicating that the starting ingredients were consumed after roughly 10–16 hours. Following the precipitation of the resultant Schiff bases and the reduction of the solvent under pressure, the sample was filtered, cleaned, and dried. This procedure was used to manufacture the following four derivatives [21-23].

Synthesis of (3R,4S,5S,6R)-6-(((2S,3R,4R,5R)-2,3,5,6-tetrahydroxy-4-((3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy) hexylideneamino) methyl) tetrahydro-2H-pyran-2,3,4,5-tetraol [1]

6-deoxy-6-amino-D-glucose (0.2g, 1.12 mmol) was reacted with D-lactose (0.38 g, 1.1.2 mmol) according to the general procedure mentioned in (2.1.5.) to yield a yellow crystal of compound [**1**] (0.4g, 0.73 mmol, 71.30%) m.p. (113–115 °C).

See Fig. 3 for ^{1}H-NMR spectrum and Fig. 4 for ^{13}C-NMR spectrum.

Synthesis of (3R,4S,5S,6R)-6-(((2S,3R, 4R,5R)-2,3,5,6-tetrahydroxy-4-((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxyl methyl) tetrahydro-2H-pyran-2-yloxy)hexylideneamino)methyl)tetrahydro-2H-pyran-2,3,4,5-tetraol[2]

6-deoxy-6-amino-D-glucose (0.2g, 1.12 mmol) was reacted with D-maltose (0.38 g, 1.12 mmol) according to the general procedure mentioned in (2.1.5.) to yield a yellow crystal of compound [**2**] (0.43g, 0.85 mmol, 716.64%) m.p. (112–116 °C).

See Fig. 5 for ^{1}H-NMR spectrum, and Fig. 6 for ^{13}C-NMR spectrum.

Synthesis of (2R,3R,4R,5S,Z)-3-((3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)-6-((3R,4R,5S,6R)-2,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-3-ylimino)hexane-1,2,4,5-tetraol [3]

2-deoxy-2-amino-D-glucose (0.2g, 1.12 mmol) was reacted with D-lactose (0.38 g, 1.12 mmol) according to the general procedure mentioned in (2.1.5.) to yield a yellow crystal of compound [**3**] (0.425g, 0.84 mmol, 75.75%) m.p. (109–114 °C).

See Fig. 7 for ^{1}H-NMR spectrum, and Fig. 8 for ^{13}C-NMR spectrum.

Synthesis of (2R,3R,4R,5S,Z)-3-((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)-6-((3R,4R,5S,6R)-2,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-3-ylimino)hexane-1,2,4,5-tetraol[4]

2-deoxy-2-amino-D-glucose (0.2g, 1.12 mmol) was reacted with D-maltose (0.38 g, 1.12 mmol) according to the general procedure mentioned in (2.1.5.) to yield a yellow crystal of compound [**4**] (0.42g, 0.83 mmol, 74.75%) m.p. (112–116 °C).

See Fig. 9 for ^{1}H-NMR spectrum, and Fig. 10 for ^{13}C-NMR spectrum.

Material and Methods

Staphylococcus aureus and *Staphylococcus epidermidis* isolates were cultured on blood agar; *Pseudomonas aeruginosa* and *Escherichia coli* isolates were cultured on MacConkey agar[24, 25].

MacFarland Turbidity Standard

The calibrated solution from the business Biomeriex was utilized to determine the approximate amount of bacterial cells, yielding 1.5 x 108 cells/m[26, 27].

Muller Hinton Agar

This medium was prepared by dissolving 38g in one liter of distillated water, and it was then autoclaved at 121 degrees Celsius for fifteen minutes while applying 15 pounds of pressure. After cooling, it was transferred to sterilized dishes and refrigerated until needed[28].

Determination the Antimicrobial Activity by Agar Well Diffusion Method

To create the suspended bacteria, several bacterial colonies were loop-transported, and the bacteria were then activated by placing them in tubes containing brain-heart infusion broth. The tubes were incubated at 37 °C for 18 to 24 hours. A comparison was made between the suspended bacteria and the conventional MacFarl and solution (1.5 x 108) cells/ml. Subsequently, the suspended bacteria were dispersed using a sterile swab, placed onto Muller-Hinton agar plates, and allowed to air dry on the plate. The culturing media was punctured using a sterile corn borer. Using a micropipette, 100 µl of the substance (25, 50, and 100 mg/ml) was applied to each hole separately. For every plate, a disk containing penicillin (PG 10 µg) was added. The diameter of the inhibition zone surrounding each hole was measured in order to assess the efficacy of each concentration[29, 30].

Results and Discussions

A valuable class of chemical substances, glucose has numerous uses in the pharmaceutical and medical industries as well as other areas of life. Glucosamine plays a critical part in the treatment of arthritis and is also utilized as an anti-microbial, anti-viral, anti-fungal, and anti-cancer agent. This study was created with the goal of discovering new analogs with superior properties. There were two glucosamine classifications in use: Reducing disaccharides, maltose and lactose, were selected as the synthesis precursors, whereas 2-deooxy-2-amino-D-glucose and 6-deoxy-6-amino-D-glucose were used as starting materials. Because the starting materials and synthesis precursors have the carbonyl and amine groups—chemical functional groups needed for Schiff coupling in an aqueous solution—they were chosen for their accessibility, affordability, biodegradability, and availability.

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D-lactose and D-maltose are suggested to have a cyclic structure (chair or boat forms) to avoid steric hindrance, but in Schiff reaction solution they are subjected to mutarotation or anomerization or a change in the equilibrium of α and β anomers through the open chain which give in opportunity to Schiff reaction to occur (Figure 1).

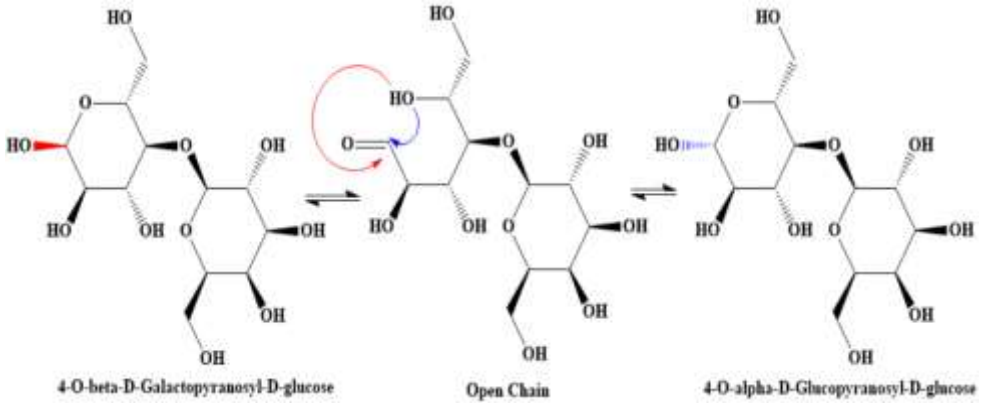

Figure 1: Mutarotation of D-Lactose

The reactions of 6-amino-6-deoxy-D-glucose are shown in Scheme 1. Simple Schiff reactions were applied to (6-ADG) with both D-lactose and D-maltose to yield (3R,4S,5S,6R)-6-(((2S,3R,4R,5R)-2,3,5,6-tetrahydroxy-4-((3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy) hexylideneamino) methyl) tetrahydro-2H-pyran-2,3,4,5-tetraol [**1**] and (3R,4S,5S,6R)-6-(((2S,3R, 4R,5R)-2,3,5,6-tetrahydroxy-4-((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxyl methyl) tetrahydro-2H-pyran-2-yloxy)hexylideneamino)methyl)tetrahydro-2H-pyran-2,3,4,5-tetraol [**2**], respectively, While the reaction of 2-deoxy-2-amino -D-glucose with the targeted disaccharides are produced compound (2R,3R,4R,5S,Z)-3-((3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)-6-((3R,4R,5S,6R)-2,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-3-ylimino)hexane-1,2,4,5-tetraol [**3**] and compound (2R,3R,4R,5S,Z)-3-((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)-6-((3R,4R,5S,6R)-2,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-3-ylimino)hexane-1,2,4,5-tetraol [**4**] respectively, as shown in Scheme 2

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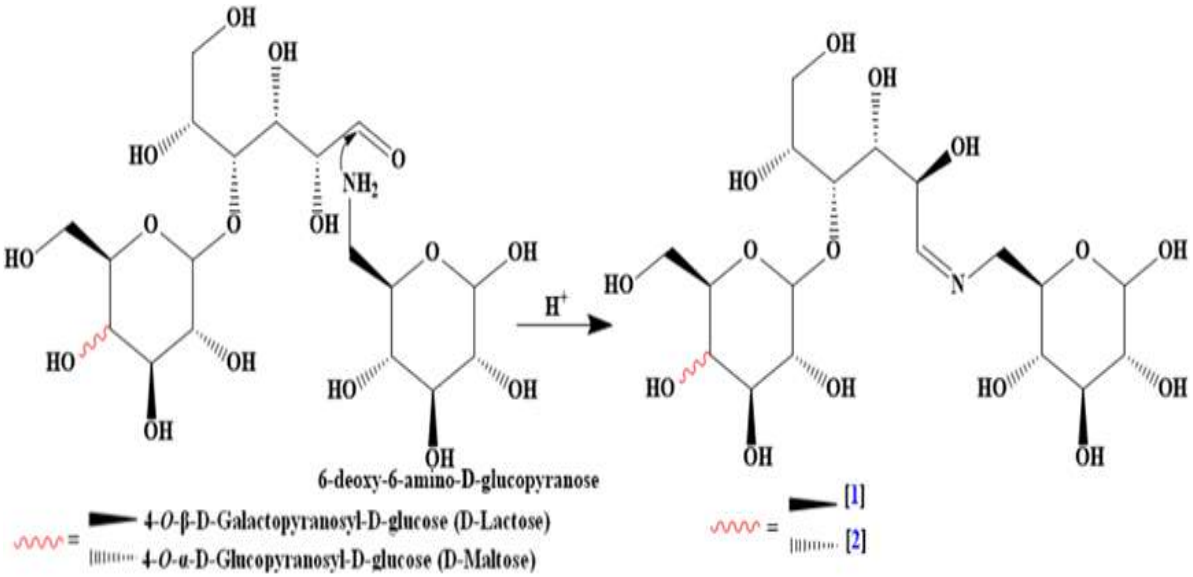
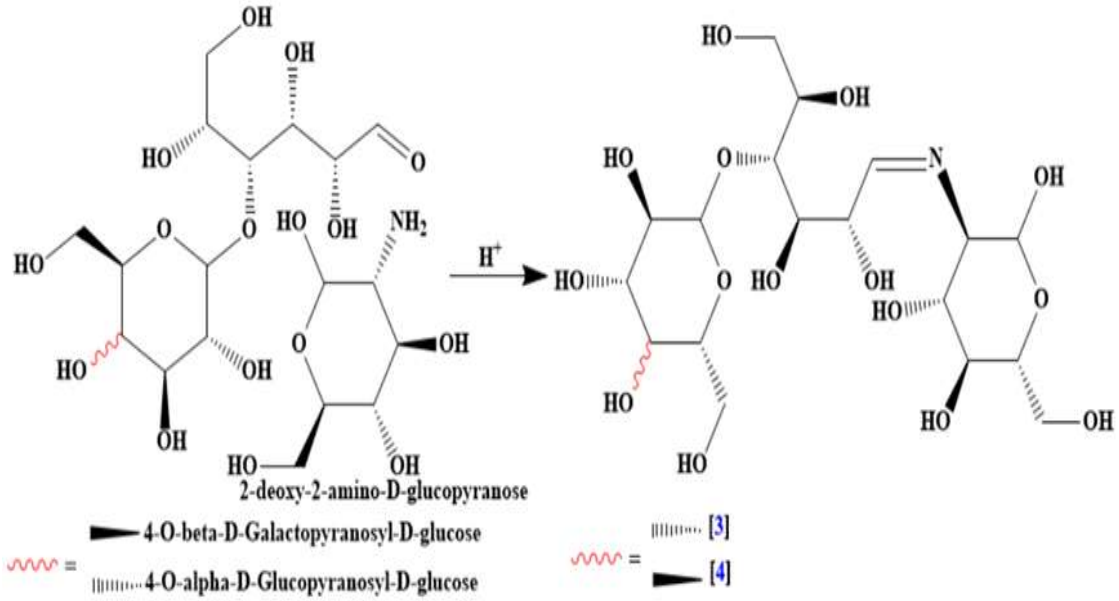


Scheme 1: Synthesis of Compounds [1] and [2]



Scheme 2: Synthesis of Compounds [3] and [4]

There are optical isomerization (R, S configurations) found in compounds [**1**] and [**2**], as both have chiral centers (chiral carbons or asymmetric carbons), and as a result, they have mirror image enantiomers (Figure 2).

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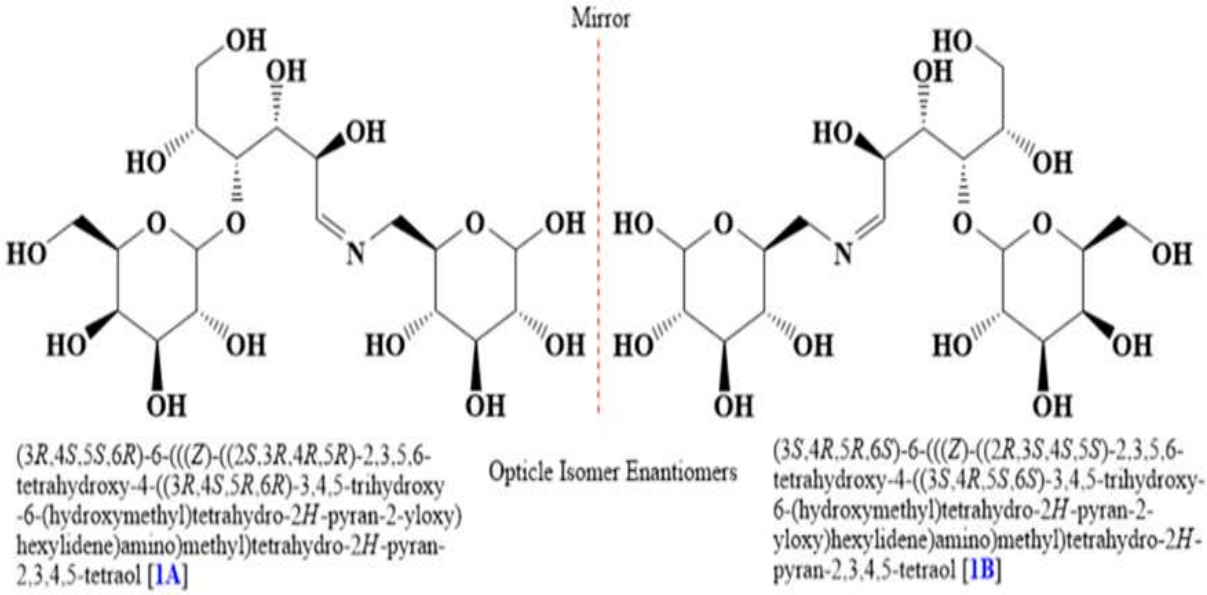

Figure 2: R, S Configuration of Compound [1]

Isomerization (R, S isomers) and anomerization (α, β anomers) reflexed clearly in the ^{1}H-NMR spectrum for compound [**1**]. Four peaks appear at δ 6.69-6.21 with integration equal to one proton for the imine proton; the two double doublet peaks at δ 6.35-6.33 and δ 6.22-6.21 represented R and S isomers (approximately about 50% for each), while the two small doublet peaks at δ 6.69-6.66 and δ 6.60-6.57 represented the α and β anomers (the ratio of β, α anomers is about 73% to 27%, respectively) as the β anomers are more stable than α due to steric hindrance. The anomeric proton of the galactose moiety appears at about δ 5.11-5.10, for the glucose moiety at δ 4.92-4.92, the secondary hydroxyl groups at δ 4.85-4.47, the primary hydroxyl groups at δ 4.39-4.18, and other protons at δ 3.74-2.89 (for more details, see Figure 3).

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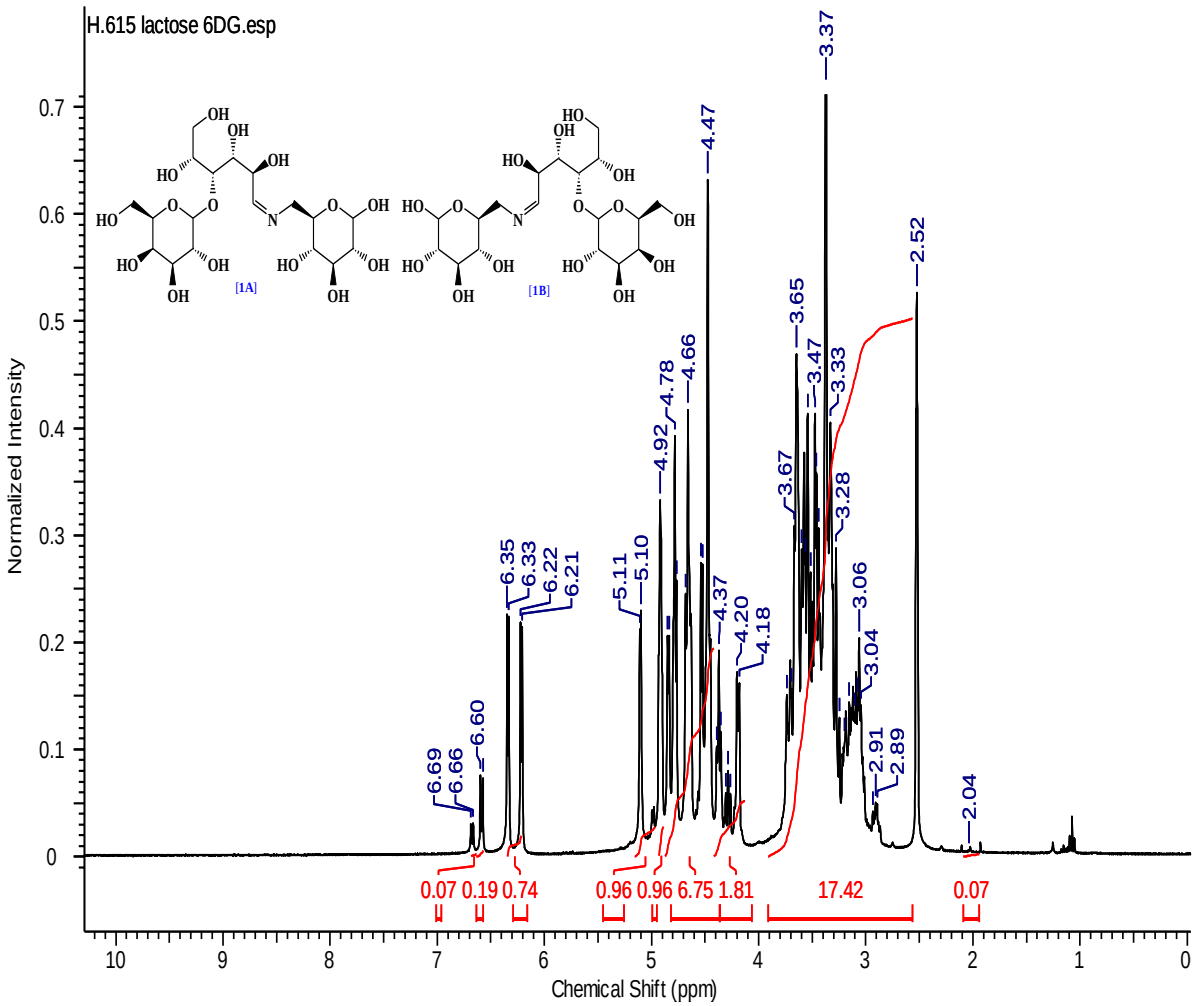

Figure 3: ^{1}H-NMR of Compound [1]

The ^{1}H-NMR spectrum for compound [**2**] shows that four peaks appear at δ 6.71-6.22, with integration equal to one proton for the imine proton. R, S isomers imine proton signals are shown at about δ 6.61-6.59 and δ 6.23-6.22; the signals of α, β anomers are listed at δ 6.71-6.68 and δ 6.37-6.35, but the ratio of each is about 50%. Other peaks approximate the same chemical shift of the compound [**1**] (for more details, see Figure 4). ^{13}C-NMR spectra for compounds [**1**] and [**2**] show the chemical shift of imine carbon at δ 104.31-104.32, anomeric carbon at δ 92.00-80.00, and other carbon atoms appearing in between δ 77.00-60.00 (for more details, see Figures 5 and 6).

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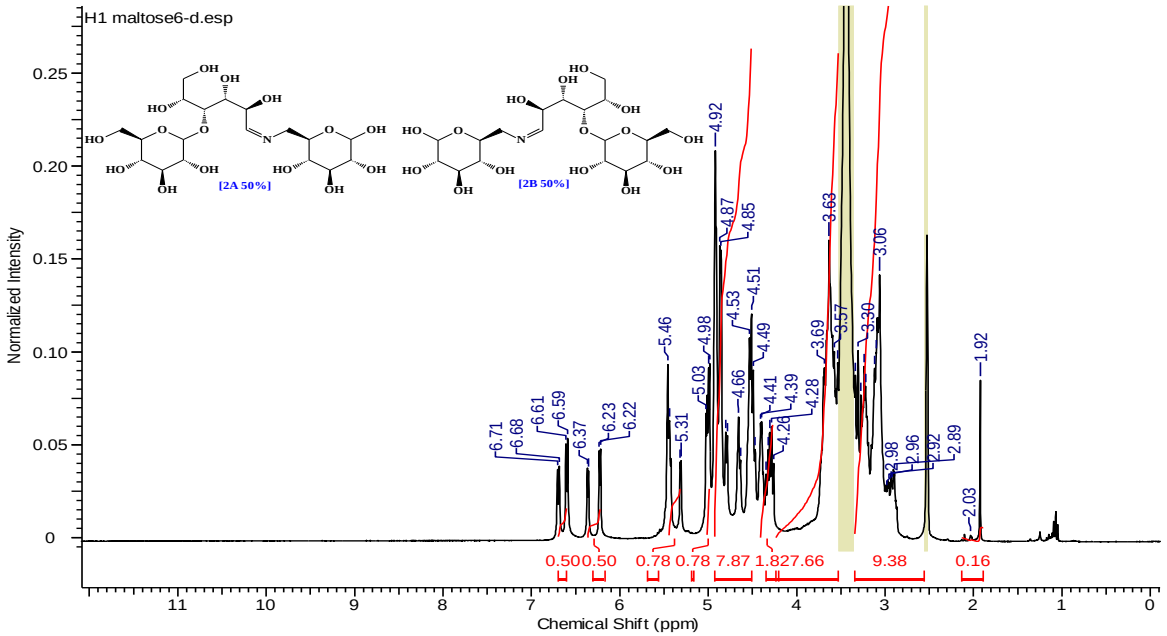

Figure 4: ^{1}H-NMR of Compound [2]

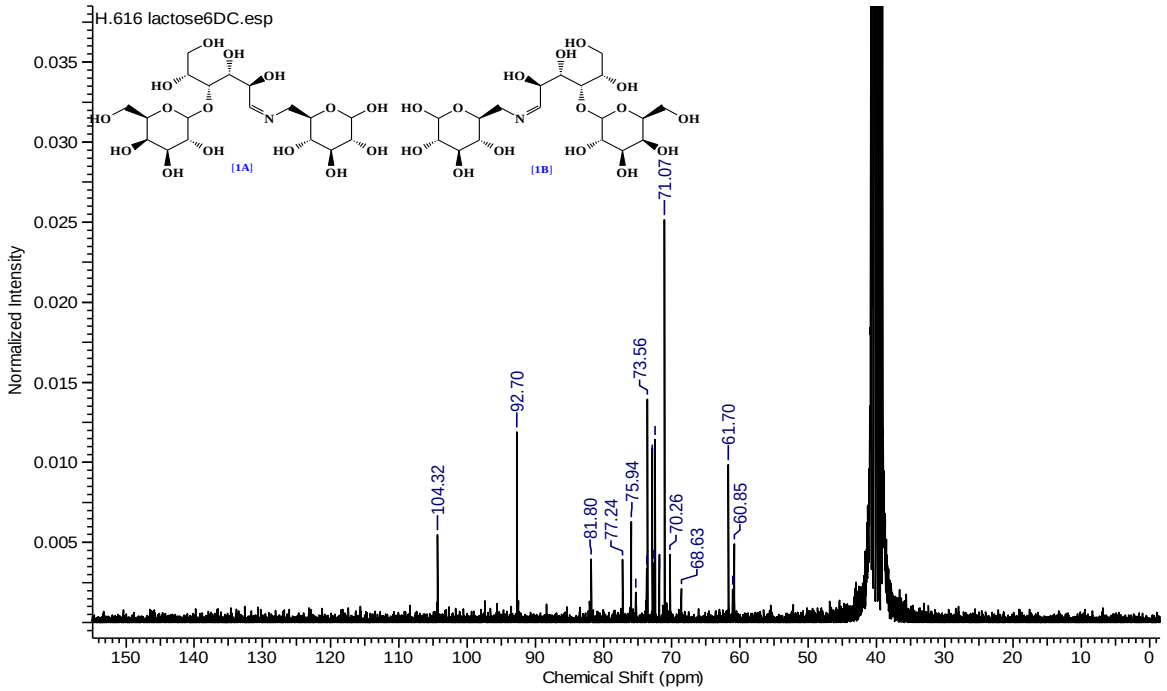

Figure 5: ^{13}C-NMR of Compound [1]

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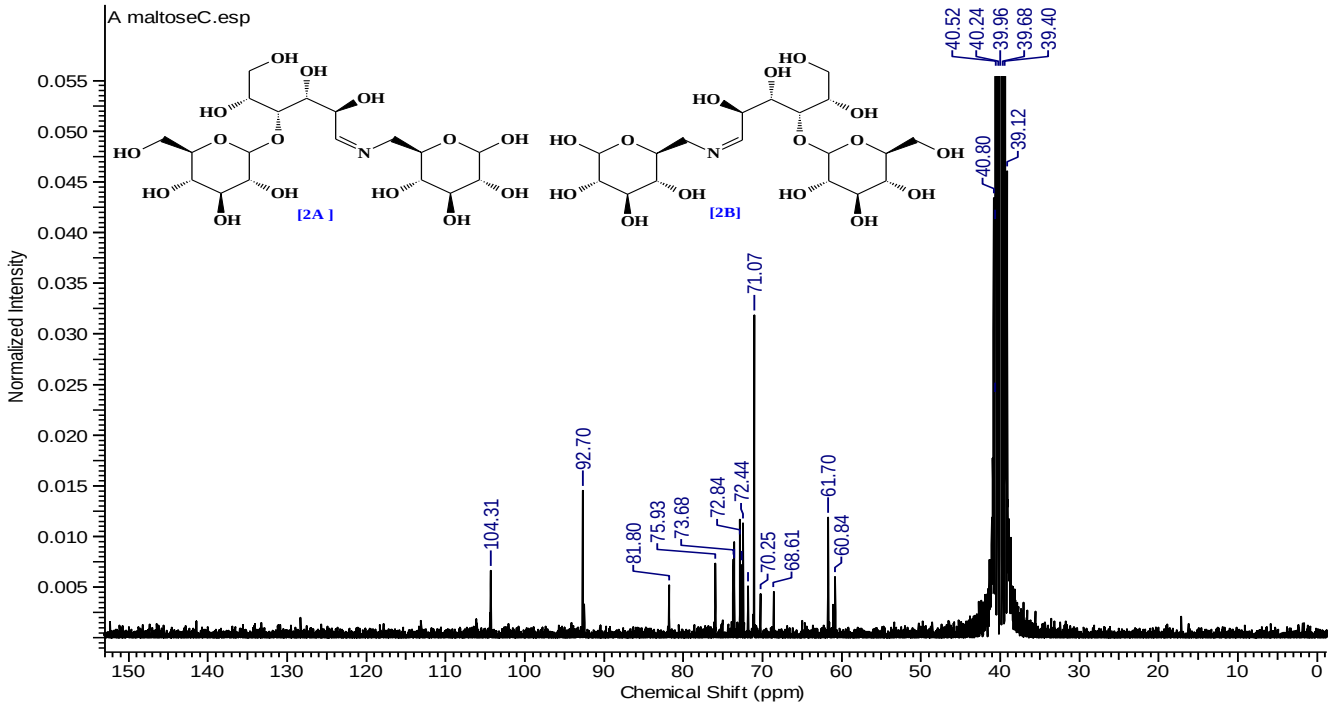

Figure 6: ^{13}C-NMR of Compound [2]

The ^{1}H-NMR spectra for compounds [**3**] and [**4**] show the four signals of imine proton at δ 6.71-6.22 as described in compound [**2**] exactly; other peaks appear at their expected chemical shift in both ^{1}H-NMR and ^{13}C-NMR, which proves the characterization and purity of the synthesized compounds (for more detail about 1H-NMR and 13C-NMR, see Figures 7, 8, 9, and 10).

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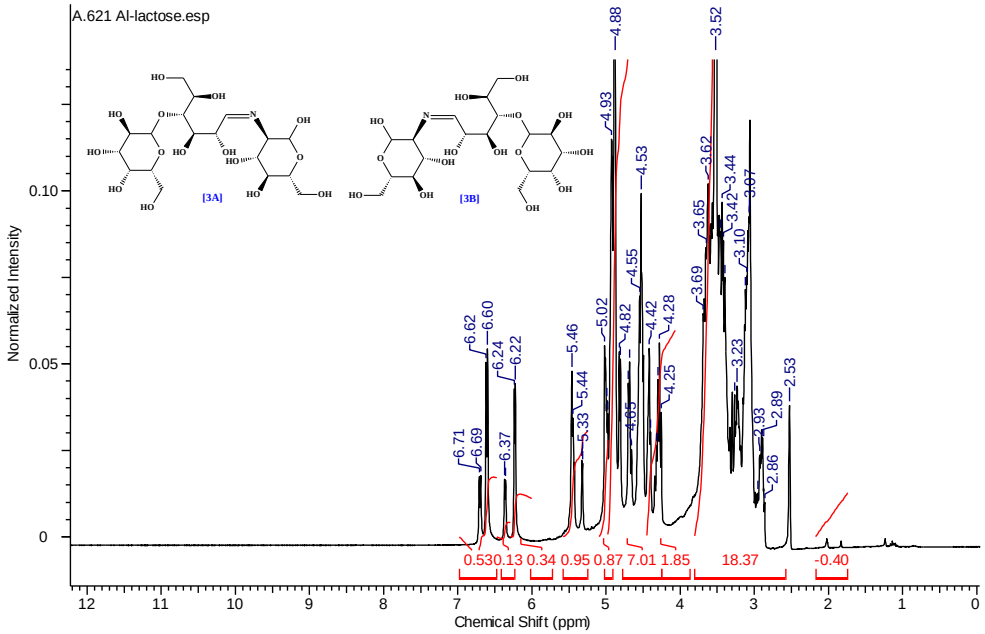

Figure 7: ^{1}H-NMR of Compound [3]

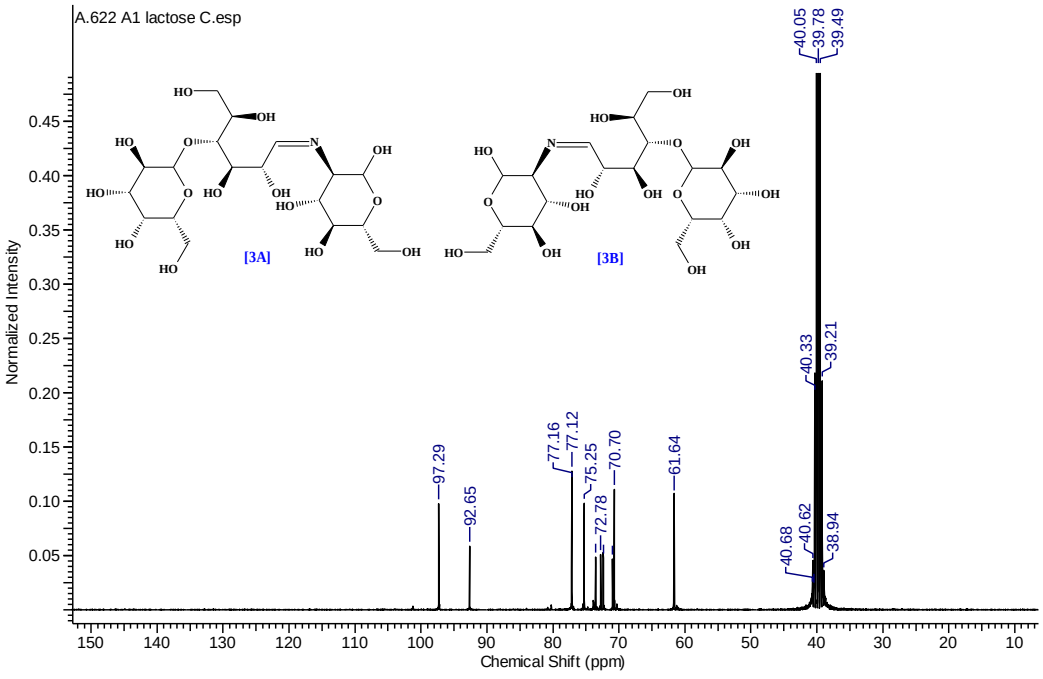

Figure 8: ^{13}C-NMR of Compound [3]

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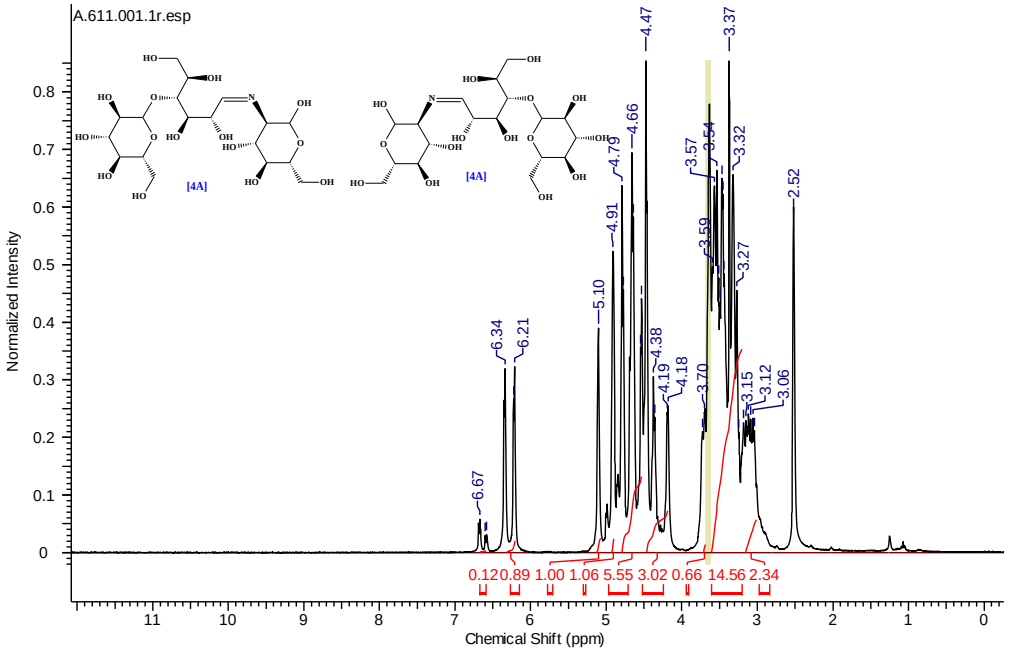

Figure 9: ^{1}H-NMR of Compound [4]

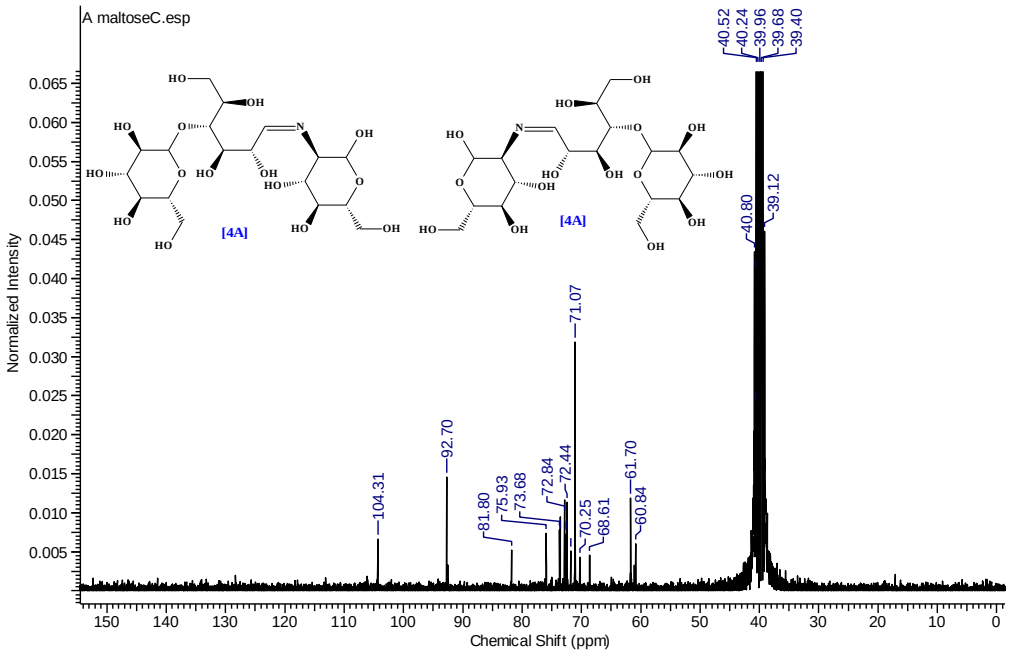

Figure 10: ^{13}C-NMR of Compound [4]

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The IR spectra of compounds [1-4] are used primarily to prove the structure of the target compounds. The appearance of the unique peaks of the amine group that participate in all synthesized compounds is the imine group, which appears between 1645 and 1690 cm^{-1}, in addition to the hydroxyl group O-H stretching, hydrogen-bonded stretching (3500–3200 cm^{-1}), and alkane groups C-H stretching (3000–2850 cm^{-1}), C-H bending, or scissoring from 1470–1450 cm^{-1}, as shown in figure 11.

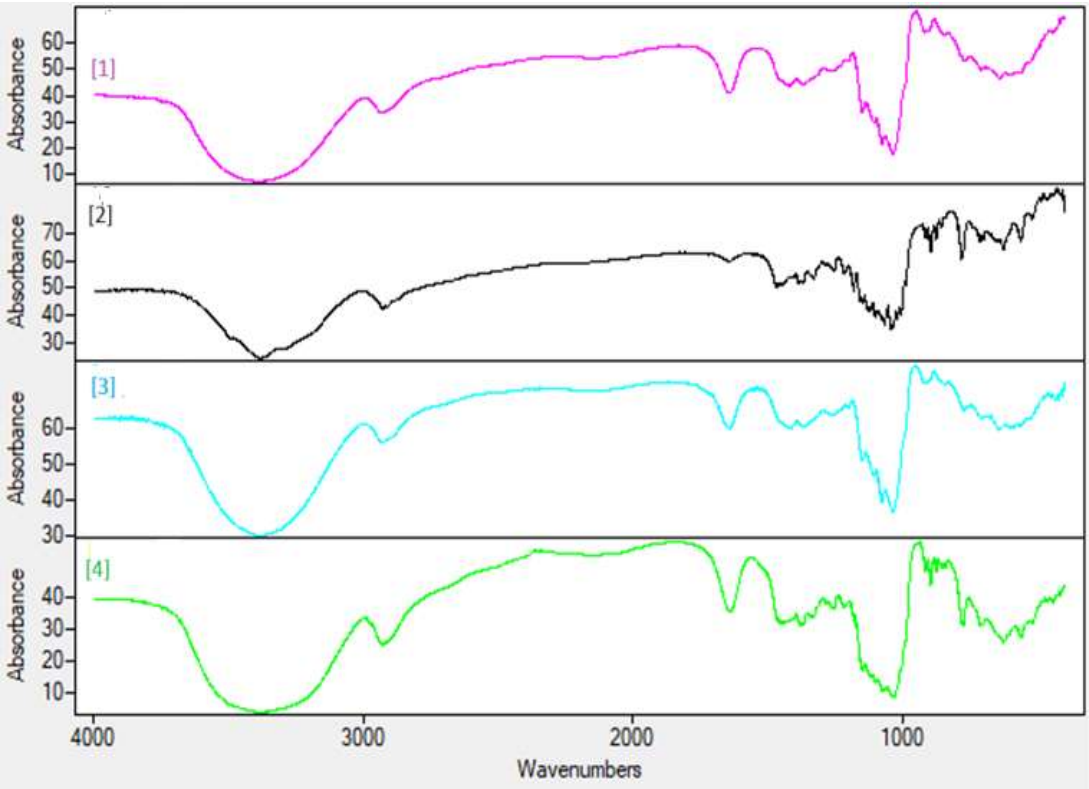

Figure 11: I R spectra for Compounds [1-4]

The biological activity of only two compounds in this series, compound [**1**] and compound [**2**], was tested. The test results are shown in Table 1.

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Table 1: Biological Activity of Compound [1] and [2] on gram positive and gram Negative bacteria

Com. No.	Gram positive bacteria						Gram negative bacteria					
	S. aureus			***S. epidermidis***			***E. coli***			***P. aeruginosa***		
	100	**50**	**25**	**100**	**50**	**25**	**100**	**50**	**25**	**100**	**50**	**25**
[1]	26 mm	26 mm	24 mm	21 mm	21 mm	18 mm	16 mm	0 mm	0 mm	26 mm	25 mm	22 mm
[2]	0 mm	0 mm	0 mm	0 mm	0 mm	0 mm	0 mm	0 mm	0 mm	0 mm	0 mm	0 mm
PG	0 mm		0 mm		0 mm		0 mm					
C	0 mm		0 mm		0 mm		0 mm					

Penicillin (PG) was resistant to all bacteria.

Control (C) has no biological activity in all bacteria.

Compound [**2**] doesn't show any biological activity against all gram-positive and gram-negative bacteria, while compound [**1**] exhibits high biological activity toward two of the gram-positive bacteria (*S. aureus and S. epidermidi*) in high and low concentrations and excellent biological activity toward the gram-negative bacteria (*P. aeruginosa*) in three concentrations (100, 50, and 25 mm), while exhibiting activity toward *E. coli* in just one concentration (100 mm). Both compound activities are better than references used *penicillin* (PG), which does not show any activity against the same bacteria in all concentrations used. This result can make compound [1] a candidate compound to go further in the medical and pharmaceutical fields as an analogue for the old antibiotics that became familiar to known viruses and bacteria, and there is a real need to find the replacement ones (for more details see Table 1 and Figure 11 .

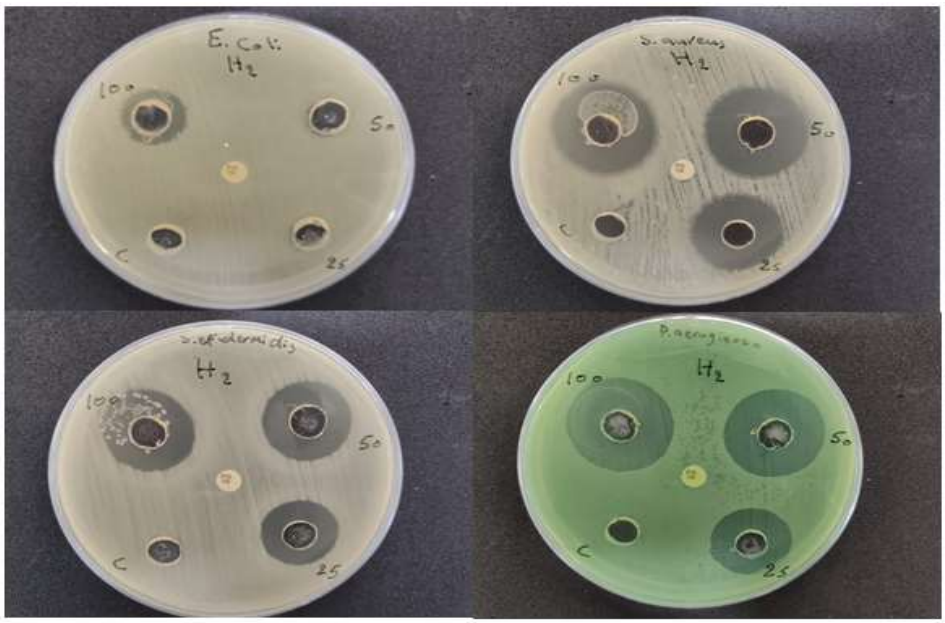

Figure 11: Biological Activity of Compound [1]

Conclusion

Glucosamine is a naturally occurring compound that shows great benefit in all fields of life, especially medicinal and pharmacological fields. In order to improve its properties, a series of four new compounds derived from glucosamine were synthesized by coupling two glucosamines, 6-deoxy-6-amino-D-glucose and 2-deoxy-2-amino-D-glucose, with two reducing disaccharides, D-lactose and D-maltose, via the Schiff reaction due to the presence of the required functional group for the Schiff reaction in both substrates. Spectroscopy proves the structure and purity of the new series. One of the two tested compounds exhibits excellent biological activity against gram-positive and gram-negative bacteria that are resistance to penicillin.

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Conflict of interest: The authors declare that there is no conflict of interest.

Ethical clearance: Ethical approval was not required for this study.

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