

Biocatalytic Potential of Enzymes Involved the Modification of Glucosamine in Chemotherapeutical Intermediates Synthesis

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Received: December 04, 2020

Accepted: February 15, 2021

Published: February 18, 2021

Citation: Senan AM. 2021. Biocatalytic Potential of Enzymes Involved the Modification of Glucosamine in Chemotherapeutical Intermediates Synthesis. *J Food Chem Nanotechnol* 7(1): 18-24.

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Abstract

The enzymatic modification of glucosamine (GlcN) and its derivatives have a keen interest for researchers due to the natural abundance of its bio-sourced such as chitin. The recent progress for understanding the role of glucosamine based on various novel approaches for enzymatic synthesis in the field of medicinal chemistry and food supplements. These developments led to improve chemo-selective protection and/or deprotection of amino-sugar during chain-enhancement and allow the simultaneous regioselective reaction of functionally relevant acetyl, phosphate, or sulfate groups. In this review, we give an overview of current strategies on the synthesis of therapeutically relevant glucosamine-containing derivatives.

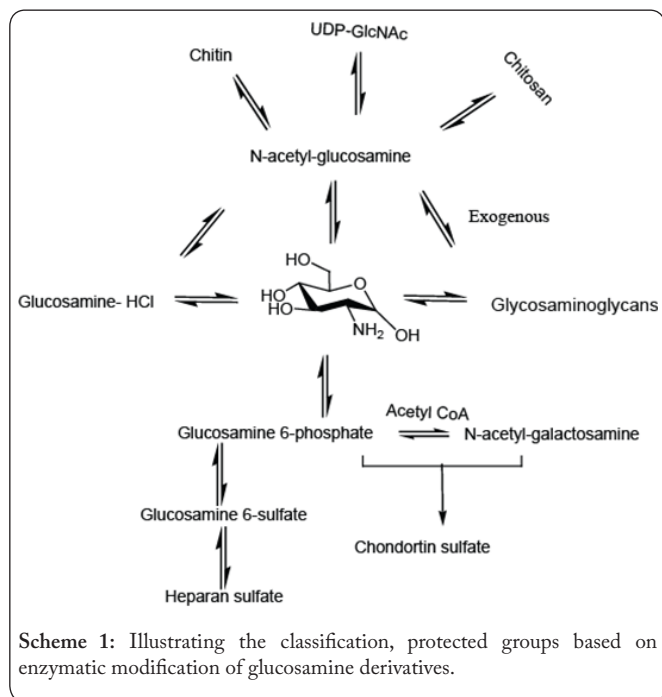
Keywords

Glucosamine, Oligosaccharides, Glycosylation, Protecting group, Biomass

Introduction

Glucosamine and its derivatives have diverse molecular structures, a prominent precursor in the biochemical synthesis of polysaccharides such proteins and lipids. In particular, N-acetyl-glucosamine and mannosamine are naturally building units of chitin which is a primary compound in exoskeletons of arthropods (Scheme 1) [1-4]. The glycosylation reaction mostly depends on the type of protecting groups; it is mostly carried out between donors-glycosyl including the acetyl glucosamine with acceptor in optimization condition in a slightly acidic medium. There are several situations in which we are concerned about the classification of approaches on the biosynthesis of oligosaccharides from GlcN derivatives [5-8].

The increasing consumption of polysaccharides as feedstock, the wide application of carbohydrates in industry and the uses of oligosaccharides as supplementary food and medicine sources are particularly well appreciated [9]. The keen interest in the pharmacological properties and the enzymatic modification of glucosamine are the main reason for its rapid growth in the production quality and the great market [10-13]. Generally, there is a proposal to succeed the modification of amino-sugars with acidic moiety and/or ester carbohydrates, including the synthesis of oligosaccharides [14-18]. In the literature, several elegant strategies have been designed to improve synthetic glucosamine's performance in nature and used as a substance-based N-X-derivatives, whereas the X instead of acetyl group, phosphate and/or polysaccharides [17, 18]. Nowadays, J. Rojo and his colleagues reported several biological modifications of carbohydrate-based on therapeutics. These advances have allowed the use of numerous

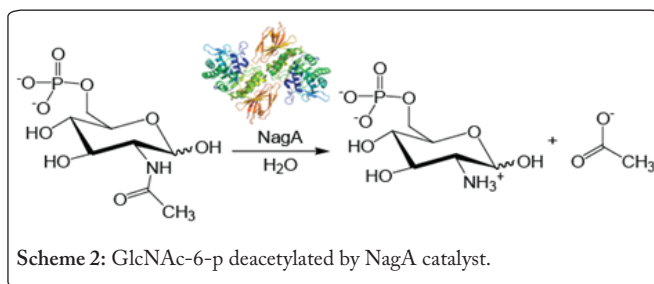


glycomimetics for drug synthesis [17, 19]. This review targets comprehensively scanning the recent developments of this exciting topic as available information, along with high coverage of modification of glucosamine [20]. Consequently, the biocatalytic modification of glucosamine derivatives can be improved via glycosylation, phosphorylation, acetylation, and synthesis of polysaccharides under some conditions: (1) β -directing effects; (2) most at an ease of attachment; (3) compatibility with the whole synthetic method; (4) facilitating NMR structural analysis due to the C2-symmetry; (5) easy reconversion and (6) the deprotection counterpart with high yield [21-25]. The most common of sugars constant amino protecting groups are collectively classified as outlined in (Scheme 1) [26-31].

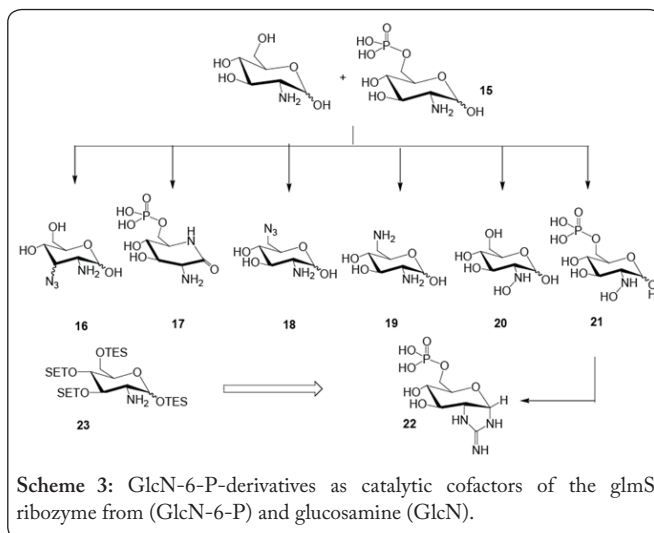
The enzymatic modification of N-acetyl- α -D-glucosamine-N-phosphate

In 1953, Leloir and Cardini reported that glucosamine produced from n-hexose 6-phosphate and N-glutamine specifically using *Neurospora crassa* enzyme in middling conditions [32]. Transformation of α -D-glucosamine-1-phosphate to N-acetyl- α -D-glucosamine-6-phosphate has been completed, and with phosphatases-catalyst to establish conversion of 6-ester. This reaction's key step is the rate limitation imposed by the chemical cleavage of phosphate and transfer within a molecule [33].

The most prevalent system of this class enzyme is called N-acetyl- α -D-glucosamine 1,6-phosphomutase (GlcNAc-1,6-p). The other names in common include acetylglucosamine phosphomutase and N-acetyl-D-glucosamine 1,6-phosphomutase (Scheme 2) [34]. NagA is known as amid-hydrolase superfamily enzyme, and it has employed for producing the amino acid, nucleic acid, and sugar through the hydrolytic cleavage of amide bonds. Increasing the nucleophilic attack on the amide bonds is activated in



present of the water as co-catalysis, and mechanistically the activation happened through the elimination of protons [35]. Adrian et al., described the GlcN and GlcN-6-phosphate are both analogues employed for supported the glmS ribozyme cofactor catalyst [36], which catalyzes site-specific phosphodiester cleavage. The enzyme GlcN-6-p synthetase (GlmS), mostly known as gram-positive bacteria, controls cell wall biosynthesis by bacterial gene-regulatory RNA (Scheme 3) [37]. The 3-azido-GlcN is produced in two chemical steps; the first step is protecting groups [1, 2, 4, 6] following the SN2 reactions mechanism with an excellent respective, and the second step is the acidic hydrolysis of an intermediate to afford the products [38-41]. The α/β 3-azido GlcN was prepared from GlcN-6-P and GlcN, the result of this performance can also give the allosamine as a rare aminosugar. The modifications of 6-OH at (GlcN-CBz.TES) protecting group, which converted to the fully deprotected by TFA/H₂O and afforded 6-azido glucosamin. Then the TES as leaving groups were hydrolyzed to produce the 2,6-diaminoglucose analogue such as the (TFA) 2 salt [40-45]. Generally, the chemical phosphorylation of the 6-OH in the GlcN analogues required N-protecting groups. An oxaziridine was utilized as starting materials to prepare the 2-hydroxylamino-glucose analogue, which could be converted to its 6-OH precursor. There action with enzymatic phosphorylation procedure carried out to give the 6-phospho- 2-hydroxyl-aminoglucose.

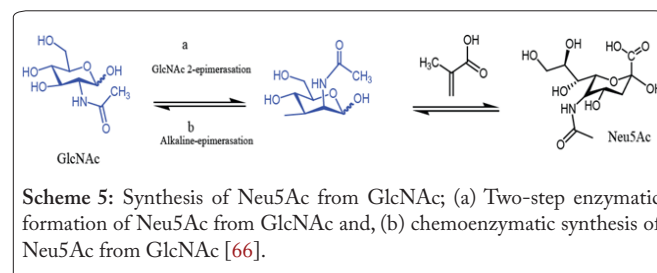


However, the particularity is almost certainly non-existent but afforded the 2-guanidiny-glucose as intermediate of the 6-phospho analogue after final deprotection. Furthermore, treating through 6 steps including the yeast hexokinase

in presence ATP, is used to produce 6-phospho-2-hydroxyl aminoglucoseanalogues with 6-OH-compounds, which was unstable under simple conditions [46, 47]. The preparation of 6-phospho-2-aminoglucolactam 17 from glucosamine was synthesized far away in 13-steps as long as procedures in literature [44]. The phosphorylation stage is mostly executed with POCl₃ in pyridine, and the selectively exposed 6-OH group included the triethylsilyl (TES) protecting group. The movement of the leaving groups was achieved in late 2-step, this enhancement of selectivity for producing phosphate group in sugaramine-6-OH [48-50].

The preparation of tri-O-acetyl-D-glucal occurs in one pot without separation of the intermediate products. Tri-acetyl glucal was obtained in good yield by Dhurandhareetal [51]. In general, the anomeric protection can be followed the traditional protection and deprotection strategies, including peracetylation of azido hexose and its variety of oligosaccharide [52, 53]. Most recently, our research group unexpectedly has been found a new approach for obtaining glucosamine from chitin under simple conditions. Using the deacetylase enzyme which isolated from *Cyclobacterium marinum* and these can all be used to convert the GlcNAc to glucosamine following two-steps strategies: (a) glycosidic bond cleavage of chitin to give intermediate GlcNAc by enzymatic processes, and (b) through selective enzyme which has ability for N-deacetylation GlcNAc to GlcN with high yield (Scheme 4) [54]. The GlcNAc is particularly obtained with acidic hydrolysis of chitin as in (Scheme 4), the GlcNAc converted to GlcN as

promotional effects were also observed in several related biocatalysts that modified GlcNAc-6-phosphate to GlcN-6-Phosphate. Anderson and his colleagues used the method to make glucosamine fungal as a microbial biomass resource (Scheme 4) [63].



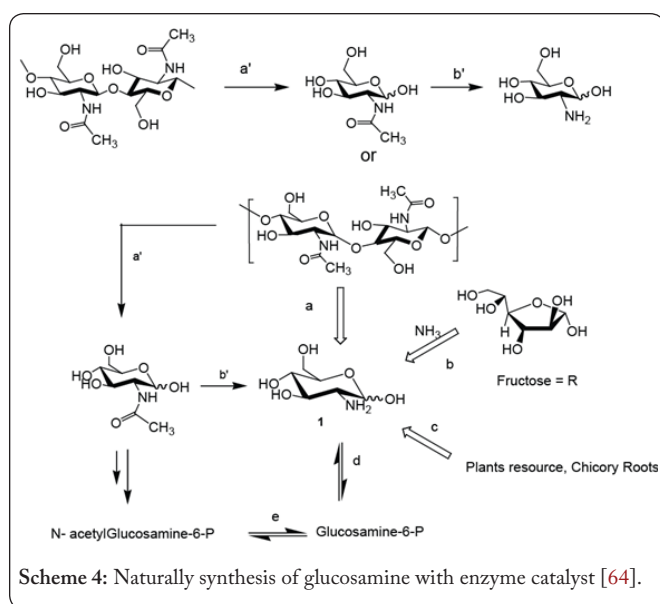
All methods of previous studies were required harsh conditions such as concentration acidity, high temperature, resulting in low yields and mostly no more than 50% conversion. However, the improvement of biocatalyst for the direct N-deacetylation of GlcNAc is described by our research group. The obtaining of the GlcN from chitin has also been investigated and was compared with de-N-acetylation efficiencies of previous methods [64, 65]. However, a biocatalytic reaction is usually unlike a Lewis acid catalyst in a chemical synthesis process. A biocatalytic reaction would possibly result in a one-pot synthesis process with a low cost and good economy. The enzymes are significantly playing a role in biocatalytic reactions, it is improved the activation, modification, and control of enzymatic catalysis's efficiency.

The chitin and chitosan are found as biomass components in the cell wall of crustaceans and insects, this converted by using different biochemical process; an enzymatically deacetylated and hydrolyzed the chitin to form a GlcN [66-70].

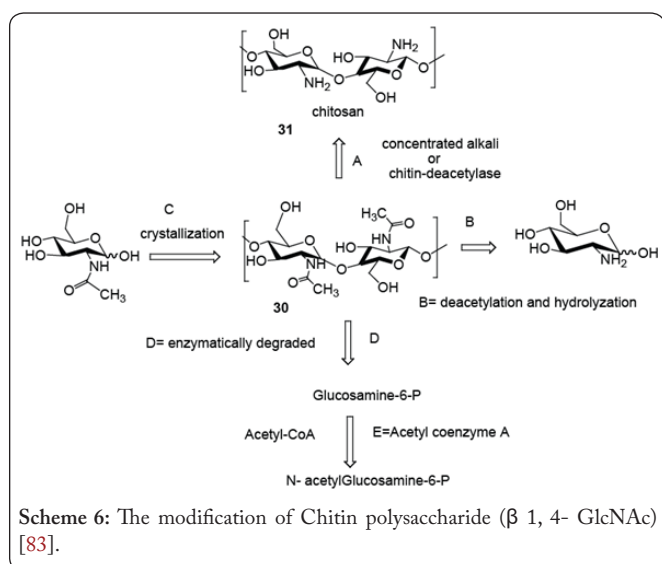
Bio-catalytic transformation of biomass to glucosamine derivatives

In literature were concluding the polymerization of Glucose/GlcNAc to synthesize polysaccharides cellulose/chitin, respectively. A chitinase is used as a key biocatalytic modification of chitin to chitosan through deacetylated procedure. The more important steps that the conversion of chitin to the primary glucosamine by de-N-acetylation/hydrolyzation of chitin (B) enzymatic crystallization of GlcNAc to obtained the chitin (C) [67]. The biodegradation of biomass is accessed to obtain the necessary intermediate compounds of GlcN-6-P [71-78]. Similarly, procedure B is carried out by deacetylation- hydrolyzation method scheme 6. Whereas the chitin is enzymatically degraded and phosphorylated to form the derivatives of GlcN-6-P, such as in steps D, which can be converted to N- acetyl-glucosamine-6-P in presence acetyl coenzyme A (E) [79-83].

The modification scope of glucosamine derivatives and its classification of protecting amino groups have been described along with their advantages/disadvantages, involving the synthesis of diverse polysaccharides either from mono/di-chloro-N-acetyl-glucosamine and/or N-acetyl glucosamine-



intermediate [51, 55-58]. However, Petiard et al. [59] reported that the extraction of GlcN from plants investigated with high temperature and low yield (Scheme 4). In the literature, the synthesis of glucosamine-6-phosphate said by David H. Brown [60], that the D-glucosamine-6-phosphate in aqueous solutions of the ester is not stable, it found as mixture product with GlcN compound (Scheme 4) [61, 62]. The biocatalyst is used for deacetylation in mild reaction conditions. Similar



HCL. Furthermore, the glycosylation reaction and its mechanism described the advantages of chemical reaction of sugars degradation, acetylation and de acetylation, such as in (Scheme 6) [70, 83-87].

Conclusion

In this review, we have introduced and assessed several biocatalysis strategies related to the modification of glucosamine-derivatives, including nanotechnology and biotherapeutics such as heparin and heparin sulfate. Also, the synthesis of β -linked N-acetyl-D-glucosamine-containing oligosaccharides was illustrated. The classification of protected groups based on enzymatic modification from glucosamine to glycosides. Specifically, in the chemical formulation of the glucosamine and/or the oligosaccharides-D-glucosamine containing nitrogen atom that can be masked as part of an amino-protecting group or latent amino group. This review allows the readership to clearly understand how components of glucosamine derivatives with various reagents and oligosaccharide synthesis become therapeutics. In particular, the understanding of the relationship between multiple functionalities, stereochemistry, and the related biological activity will help researchers to design and improve their chemical synthesis of target saccharides in nearly future.

Conflict of Interest

The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

Acknowledgments

This work was supported by the NJAU Academia and Department of Food Science and Technology, which start-up initiative of the 1000 Foreign Talents Plan (grant number 8080 to Ahmed M.).

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