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Trends in Carbohydrate Research

An Overview of *N*-Glucopyranosylamine-derived Molecules

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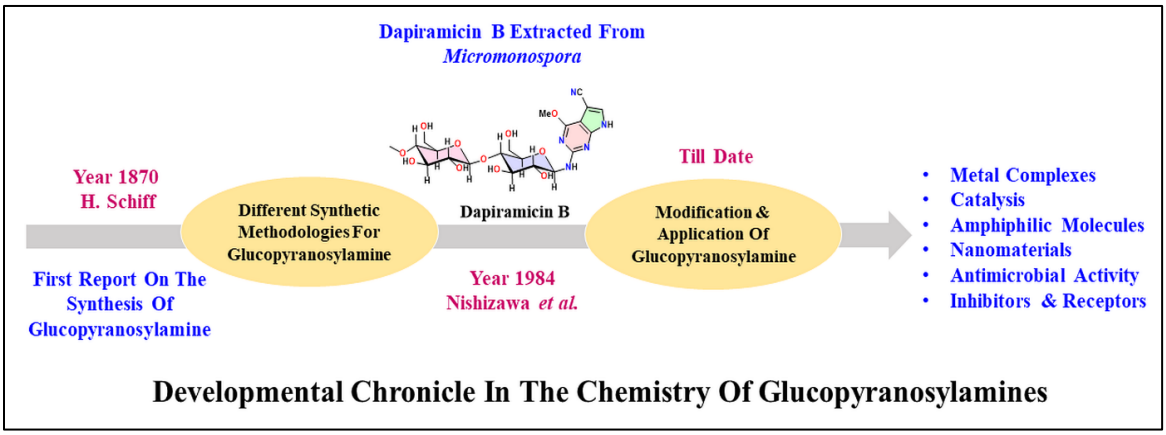
Graphical Abstract



Abstract

N-glycosylamines are important compounds from chemical, biological as well as pharmaceutical point of view due to their presence in glycoproteins and nucleic acids. This review describes the details of synthetically developed *N*-glycoconjugates of D-glucose and their stability. The reactivities and applications of glucopyranosylamine derivatives in the form of metal chelation, drug delivery, molecular sensing etc. have been summarized here.

Keywords: Glucopyranosylamine; *N*-Glucoconjugates; Glucolipids; Glucopeptides; Inhibitors

1. Introduction

About two-thirds of the carbon in the biosphere is present in various forms of carbohydrates like polysaccharides, nucleic acids and antibiotics.[1] Among these molecules, glycosylamines are widely present in the form of nucleic acids, glycoproteins etc. Due to biological relevance, glycosylamines attract the attention of synthetic chemists, biologists, and pharmacists. These molecules are considered as active site directed reversible inhibitors of glycosidase[2-3] and are widely used in agrochemicals and pharmaceuticals as antibacterial and antifungal agents.[4-5] Due to the vast coverage, this review is confined to the details of glucopyranosylamine derivatives only, where glucose contains C1-N linkage. Even though NMR studies of D-glucose supports the presence of its acyclic and cyclic (five (furanose) and six (pyranose) membered ring) form in the solution (**Figure 1a**), glycosylamines mainly exist in pyranose form with β-anomeric configuration (**Figure 1b**). Nishizawa *et al.* isolated Dapiramicine A and B from *Micromonospora*, which contains β-D-glucopyranosyl fragment.[6] Later Noritaka Chida developed the methodology for the total synthesis of Dapiramicine B.[7] Interest of researchers from various fields of sciences have yielded the synthesis of numerous glucopyranosylamine derivatives and their application in molecular sensing, metal chelation and drug developments.

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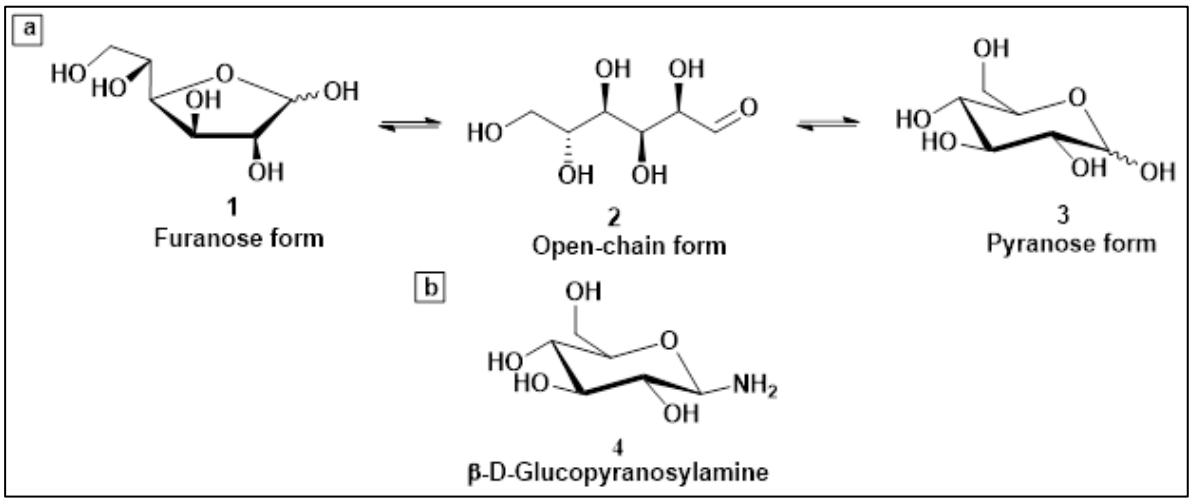


Figure 1. (a) Cyclic and acyclic forms of D-glucose in solution; (b) Structure of β-D-glucopyranosylamine.

2. Synthesis of Glucopyranosylamines

H. Schiff had reacted D-glucose with aniline and isolated a glassy, yellow-colored product during 1870, which was identified as glucosylamine.[8-9] Same reaction was repeated by Sorokin but hot ethanol was added into the reaction mixture to enhance the product yield.[10] Further, the yield was improved by heating the reactants (dextrose (10 g) and aniline (26 gm)) in ethanol (150 mL) until the glucose dissolves.[11] The *N*-phenylglucosylamine has also been synthesized by reacting aniline with tetra-*O*-acetylglucosylbromide, followed by deprotection of the acetyl group using $Ba(OH)_2$.[12] de Bruyn reacted the sugar with anhydrous methanolic solution of ammonia in warm water.[13] Latter, the yield of glycosylamines was improved by using hydrochloric acid,[14] acetic acid,[15] and ammonium chloride[16] as catalysts. Kochetkov *et al.* reacted D-glucose with an aqueous solution of ammonium bicarbonate to form the glucopyranosylamine in 66% yield,[17] while Lubineau's used saturated ammonia solution in the presence of a small quantity of ammonium bicarbonate.[18] Flitsch and Bejugam reported the reaction of D-glucose with ammonium bicarbonate in DMSO under microwave radiation to improve the reaction time and product separation process.[19]

One another approach for glucopyranosylamine synthesis includes the formation of glycosyl azides of *O*-protected sugar followed by its reduction. Zoltan *et al.* have published a review article on the synthetic strategies of glycosyl azide and their reactions in detail.[20] The glycosyl azides has been reduced by PtO_2,[21] $NaBH_4$,[22] Raney Ni,[23] Pd/C,[24] etc. to corresponding amine (**Figure 2**). The use of PtO_2 is indiscriminative between azido and *O*-allyl group, so Roger *et al.* used sodium borohydride for selective reduction of azide.[22] Azide reduction by Raney nickel is also specific, and it does not affect the benzyl-ether bond, while PtO_2 cleaves the ether linkage.[23] Roberge *et al.* have used 1,3-propanedithiol/*N*,*N*-diisopropylethylamine as selective azide reducing agent,[25] while PMe_3 in THF has been used by Marqvorsen *et al*.[26] These synthetic routes mostly yield a mixture of α/β-anomeric form of glycosylamines. Shridhar and co-workers have reported the selective synthesis of β-glycosylamine using tetrathiomolybdate as a stereo and regioselective reducing agent. This reagent reduces the azide group at C1 position only and not at C2 and/or C6 position(s).[27]

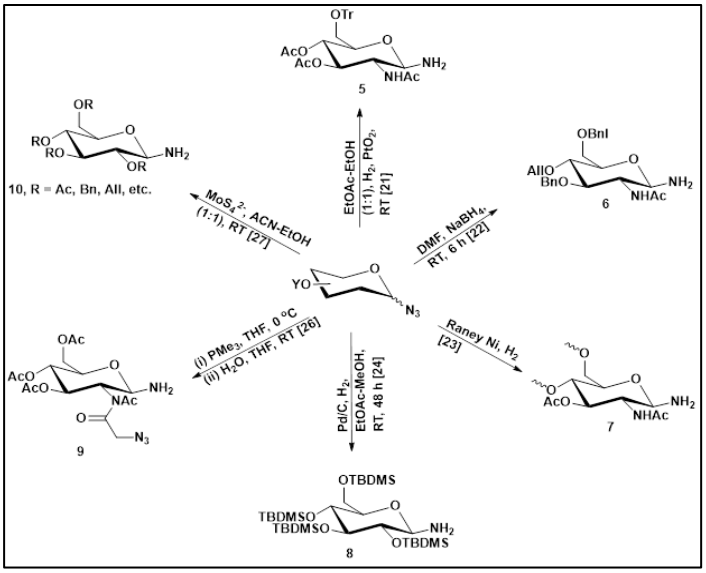


Figure 2. Different reaction conditions used for the conversion of glucosyl azides into glucopyranosylamines (Tr = trityl, Ac = acetyl, Bn = benzyl, All = allyl, TBDMS = *tert*-butyldimethylsilyl.)

Nicolaou *et al.* have used Burgess-type reagent **11** (**Figure 3**) for the stereoselective synthesis of α- and β-glycosylamine from partial *O*-protection but free C1-OH. C2-OH protection yields selectively β-anomer, while unprotected one (C2-OH) affords α-glycosylamine.[28] Gorden and Danishefsky have reported the synthesis of benzyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosylamine by epoxidation of glycal followed by the reaction with benzylamine in the presence of anhydrous $ZnCl_2$.[29] Dorsey *et al.*, developed a strategy for selective synthesis of β-glucopyranosylamine starting from 2,3,4,6-tetra-*O*-benzylglucose, where sugar has been converted into δ-hydroxy nitrile *via* oxime. Reductive cyclization of nitrile by $NaBH_4$ resulted in the formation of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosylamine.[30]

Mechanochemical synthesis of glycosylamines has been reported by Lingome *et al.* in 2014, where sugars have been grinded with aliphatic and aromatic amines using ball-milling. The report elaborates the synthesis of several L-rhamnose-derived glycosylamines along with *N*-dodecylglycosylamine of D-glucose, D-galactose, and maltose.[5] Yano and coworkers have developed a number of transition metal complexes of glucopyranosylamines, where the ligands have been generated *in situ* by heating sugar and amine derivatives in the presence of metal halides.[31] 4,6-*O*-Ethylidene/butylidene/benzylidene-glucopyranose reacts with aromatic amines in alcohols to afford corresponding β-D-glucopyranosylamine under heating conditions.[32-33] These glucose derivatives also react with ammonia in the presence of catalytic amount of anhydrous zinc chloride at zero to room temperature to afford corresponding glucopyranosylamine,[34] which has been condensed with various aldehydes and acids to synthesize a large number of *N*-glycoconjugates.[35-36] Zhang and co-workers have condensed substituted aromatic aldehydes with 3-*O*-methyl-4,6-*O*-benzylidene-β-D-glucopyranosylamine for the synthesis of sugar-derived Schiff base compounds.[37] Thanh and Thoa had reacted 4,6-*O*-ethylidene-β-D-glucopyranose with substituted 2-amino-1,3-thiazoles and 2-amino-1,3-benzothiazoles to prepare corresponding *N*-glucosylamines.[38] Kulakov and co-worker have synthesized halogen-containing *N*-glucosylamines by reacting D-glucose with 4-bromo-3-methylaniline, 2,4,6-tribromoaniline, and 2-amino-5-bromopyridine.[39]

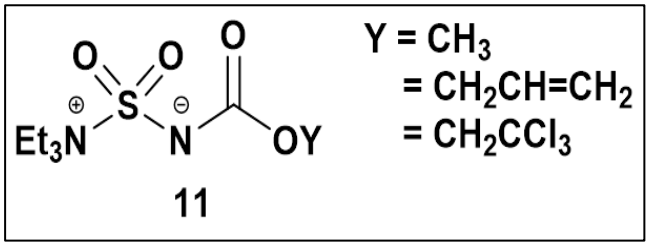
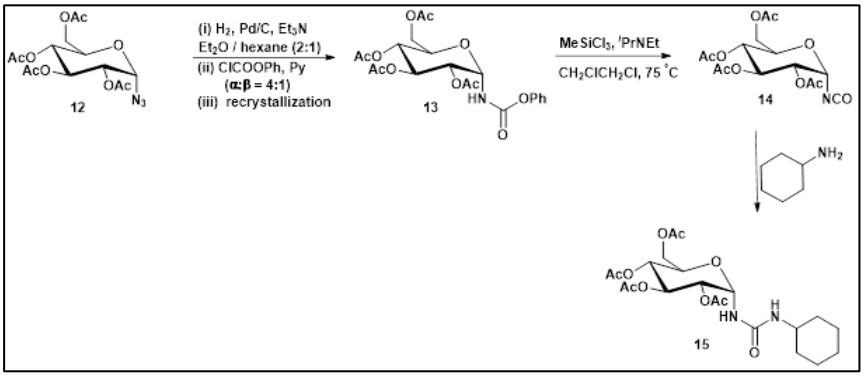


Figure 3. Structure of Burgess type reagent.

3. Glucopyranosyl Urea/Thiourea and Other Heterocyclic Derivatives

Carbohydrates linked with urea and thiourea are synthetically, biologically, and pharmaceutically

important classes of molecules. D-Glucopyranosyl urea was first synthesized by condensing D-glucose and urea in aqueous media under acid-catalyzed conditions[40] and was further modified by Benn[41] and Fisher[42]. Since then, several reports have appeared on the synthesis of glucopyranosyl urea; however, they are non-stereospecific. Ichikawa and co-workers have developed synthetic protocols for the stereospecific synthesis of α- and β-glucopyranosyl isocyanates followed by their urea derivatives.[43-45] It has been noted that β-glucopyranosyl azide affords only β-form of the isocyanates, while α-anomeric form of the reactant yields a mixture of products containing both α- and β-anomers, making it challenging for the selective synthesis of α-glucopyranosyl urea.[43-44] To overcome these obstacles, several attempts were made and selective α-isomeric product was obtained *via* conversion of α-azide into glucopyranosyl carbamates **13** (**Scheme 1**).[45]



Scheme 1. Synthetic route of α-glucopyranosyl urea.

The good electrophilicity of isothiocyanates makes it a better synthon for thiourea synthesis. Fuentes *et al.* have synthesized partially protected thiourenyl saccharide **17, 21** and disaccharide **20** derivatives from isothiocyanate **16** (**Figure 4**).[46] The glucosyl isothiocyanates were also transformed into different heterocyclic derivatives **18**, **19**, and **22** (**Figure 4**).[46] Bolanos and co-workers have synthesized *O*-unprotected *N*-β-D-glucopyranosyl thiourea in a two-step procedure by reacting β-D-glucopyranosyl amine with thiophosgene followed by reaction of resultant glycoconjugate with amine derivatives.[47] Treatment of β-D-glucopyranosyl thiourea derivatives with yellow mercury(II) oxide led to the formation of 2-aminotetrahydropyrano[2,3-*d*]oxazole derivatives. The oxazole derivatives serve as biologically active molecules in treating hypertension, as appetite suppressants and inhibits pheromone synthesis.[48-49] Gergelitsová *et al.* have synthesized (thio)urea–phosphine organocatalysts containing glucopyranosylamine unit. The organocatalyst efficiently catalyzes the Morita–Baylis–Hillman reaction with good and high enantioselectivity.[50]

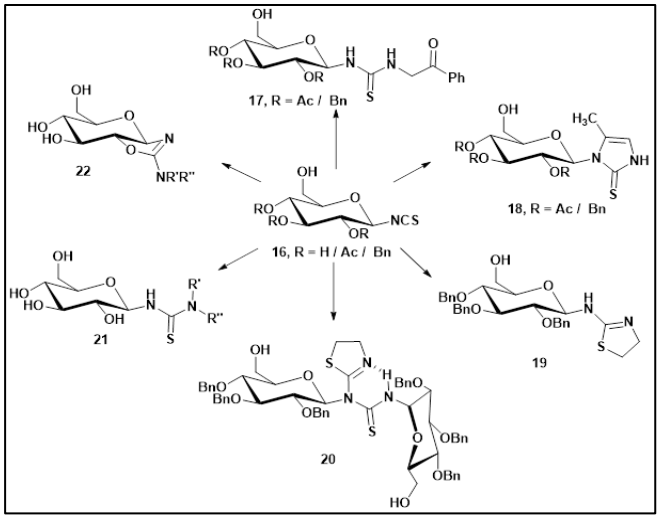


Figure 4 Transformations of glucopyranosyl isothiocyanates.

Selenosugars have also gained the attention of researchers due to the antitumor activities of seleno-compounds. The reaction of elemental Se with glycosyl isocyanide affords glycosyl isoselenocyanate in good yield, however, the product is air sensitive and unstable.[51] Bolanos and co-workers have synthesized *O*-unprotected glycosyl selenoureas by reacting β-D-glucopyranosylamine with phenyl isoselenocyanates.[52] This work was further extended to prepare the sugar-derived selenoureas and selenazoles.[53]

4. Stability and Reactivity of Glucopyranosylamines in Solution

4.1 Mutarotation, Transglycosylation and Amadori rearrangement

Glycosylamines are generally labile in solution and they undergo environment dependent mutarotation, hydrolysis, transglycosylation and Amadori rearrangement reactions.[54-57] All these reactions proceed through a common acyclic imonium ion intermediate having electron deficient anomeric carbon (C1) (**Figure 5**).[56] During mutarotation, the imonium ion acquires a pair of electrons from a hydroxyl group present in the same molecule producing a cyclic isomer (**Figure 3**). Addition of nucleophiles like hydroxyl ion or other glycosylamines to the imonium ion leads to the elimination of amine group yielding hydrolysis and transglycosylation reactions. Rates of mutarotation, hydrolysis and transglycosylation reactions along with stability of glycosylamines are dependent on pH of the solutions and the basicity of amine involved in glycosylamine formation.[55] In general, rate of mutarotation is high in the pH range 4-6 and no such reaction occurs below pH 1.5 due to the formation of stable ammonium salts.[57] Hydrolysis reaction is slow in both high and low pH conditions as it requires acid catalyst as well as a hydroxyl ion for progress of reaction. Under suitable conditions, electron deficiency of C1 is satisfied by adjacent carbon resulting in 1-amino-1-deoxyketose **28** as shown in **Figure 5**, which is known as Amadori rearrangement.[54] Progress of this reaction is highly affected by concentration of imonium ion as well as by nature of substituent on nitrogen atom.

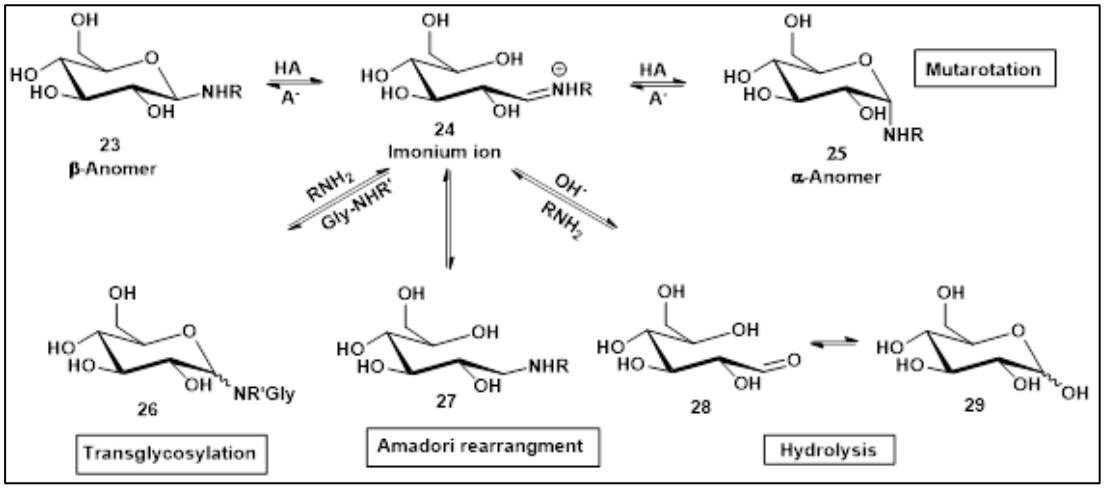


Figure 5. Mutarotation, hydrolysis, transglycosylation and Amadori rearrangement reactions of glucopyranosylamine *via* imonium ion intermediate.

4.2 Anomeric and reverse anomeric effect

The anomeric effect (AE) in carbohydrates was discovered by J. T. Edward in 1955, which brings the heteroatomic (electronegative) substituent attached with C1 at axial position.[58-60] Anomerization increases the system's stability *via* non-classical hydrogen bonding, coulombic interaction, hyperconjugation and dipole moment (**Figure 6**).[59-61]

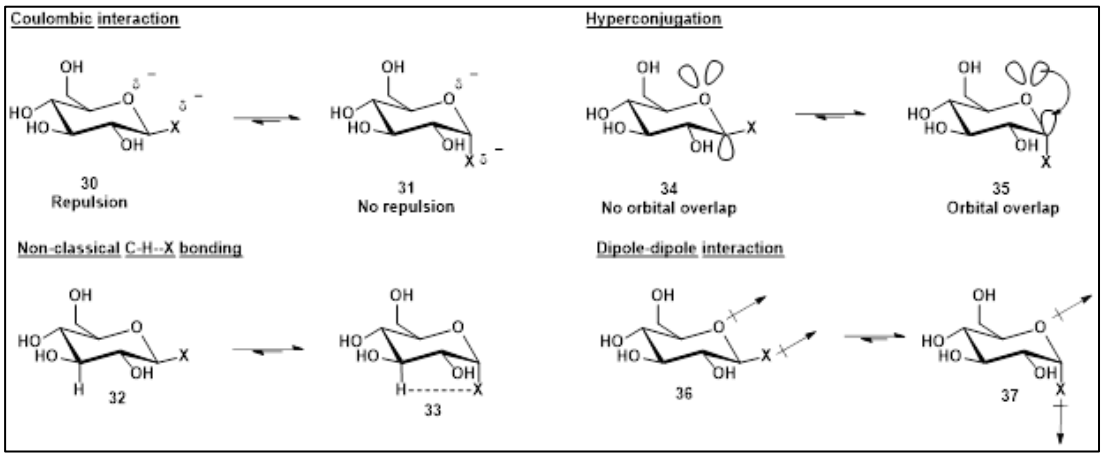


Figure 6. Driving forces for anomeric effect.

In 1965, Lemieux and Morgan observed the heteroatom at preferably equatorial position, while studies on glucopyranosyl pyridinium/imidazolium ions and in order to support this observation, a new term, "reverse anomeric effect" (RAE) was introduced.[62] Perrin *et al.,* probed glucopyranosylamine derivatives and glucopyranosylammonium ions as a model system to understand the AE and RAE, as pyridinium and imidazolium ions are too bulky for reliable assessment.[59-60] They investigated the α- and β-anomeric equilibria under different conditions (solvent, acidic, and basic media) through NMR spectroscopy. Both the α- and β-anomeric H1 was identified as a doublet having coupling constant of 5.0-5.5 and 8.5-9.0 Hz respectively. Generally, the α-anomeric H1 appeared downfield with respect to β-analogue by 0.5-0.8 ppm. The solvation of ammonium ion leads to the steric hindrance yielding excess of β-*N*-glycosides. Randell *et al.* performed the NMR study to investigate the effect of substituents and solvents on various glucopyranosylamine and their protonated form, however they could not generalize the reverse anomeric effect.[64]

A complete theory explaining the RAE has not yet been established, however few basic reasons has been suggested with their pros and cons. One theory suggests that the positive charge on nitrogen can cause a reversal of anomeric behaviour, because of the electrostatic interaction (**Figure 7a**), inversion of dipole moment (**Figure 7b**), and emergence of a negative hyperconjugation effect.[59-62] However, this theory is contradictory as the dipole moment has no significance for a group that has a net charge.[59-62] Negative hyperconjugation should increase the anomeric effect rather than reversing it. Later on, few researchers investigated the RAE in neutral molecules and observed distortion in the ring, suggesting that the RAE may be attributed to the steric repulsions of a bulky heterocyclic ring, rather than hyperconjugation within the heterocycle.

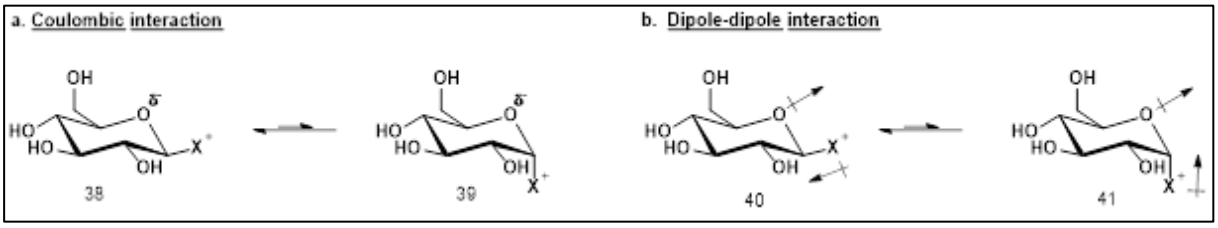


Figure 7. Driving forces for reverse anomeric effect.

Paizs *et al.* studied the configurational behavior of 1,2-*cis*- and 1,2-*trans*-cyclic carbamates/thiocarbamates of glucopyranosylamine using the *ab initio* method.[61,63] The *trans*-isomer was found to be sterically preferred over the *cis*- due to the intramolecular hydrogen bonds between NH and the ring oxygen (**Figure 8**). Batchelor *et al.* investigated the configurational preference of *N*-(4-methoxyphenyl)-2,3,4,6-tetra-*O*-acetyl-α- (α-GlcOMe) and β-D-glucopyranosylamine (β-GlcOMe) in solid as well as in solution phase.[65] They observed the α-anomeric form of α-GlcOMe in the crystal structure; however, solution studies revealed the predominancy of β-anomer. So far, extensive studies have been conducted on the reverse anomeric effect; however, a definitive explanation remains elusive.

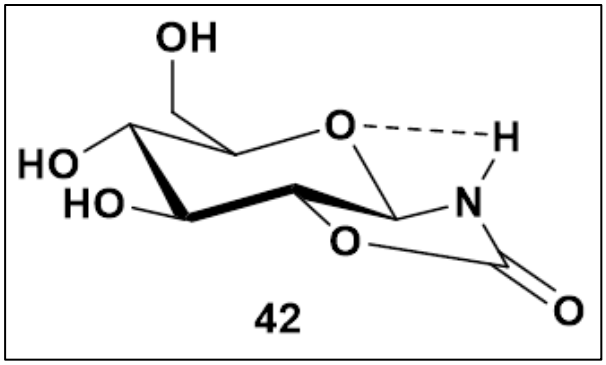
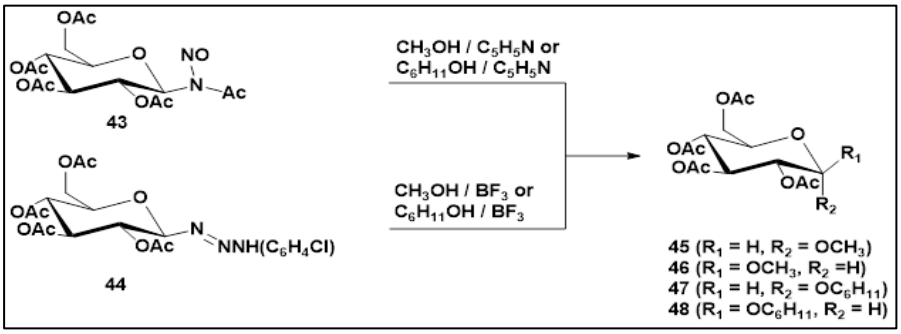


Figure 8. Structure of cyclic carbamate with hydrogen bonding (dotted line).

As mentioned above, the synthesis of α-*N*-glycosidic linkages in carbohydrate chemistry poses a significant challenge due to the prevailing thermodynamic preference for β-configuration. To address this issue, Elena *et al.* proposes the utilization of gem-diamine functionality to stabilize the α-diastereomers.[66] Their innovative approach has enabled the successful preparation of mono- and disaccharide analogs with α-*N*-glycosidic linkages.

4.3 Solvent effect on glucopyranosylamine derivatives

Glucopyranosylamine undergoes glycosidic bond cleavage *via* either S_N1 or S_N2 path in various solvents like alcohol, water, hydrazine, etc.[67-68] The specific mechanism depends on the reaction conditions and the nature of the glucopyranosylamine derivatives. Larm *et al.*, observed the anomeric mixture of products during the alcoholysis of β-*N*-glucosides (**Scheme 2**).[69]



Scheme 2. Alcoholysis of β-*N*-glucosides.

Sinnott *et al.* studied the solvolysis effect of ethanol and trifluoroethanol mixture on D-glucopyranosylamine derivatives in the presence of trifluoromethanesulfonic acid as catalyst.[70] Their studies revealed that the anomeric form of products is influenced by solvent constitution, leaving group and anomeric configuration of the starting material. Stereochemical criteria suggest unimolecular reactions with retention of configuration, but the dependence of relative rates on nucleophilicity shows bimolecular behavior. There is a weak interaction between the leaving group and the solvent molecule in the transition state (**Figure 9**) that facilitates the leaving group's departure.[70]

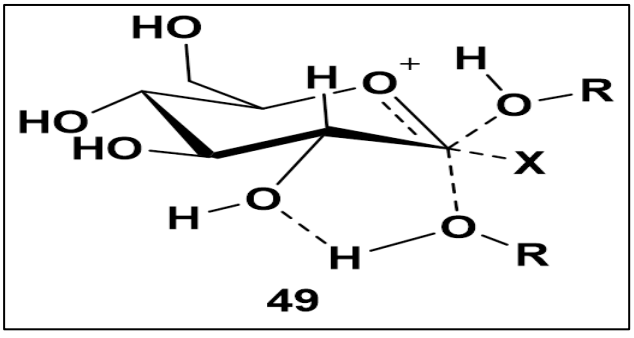
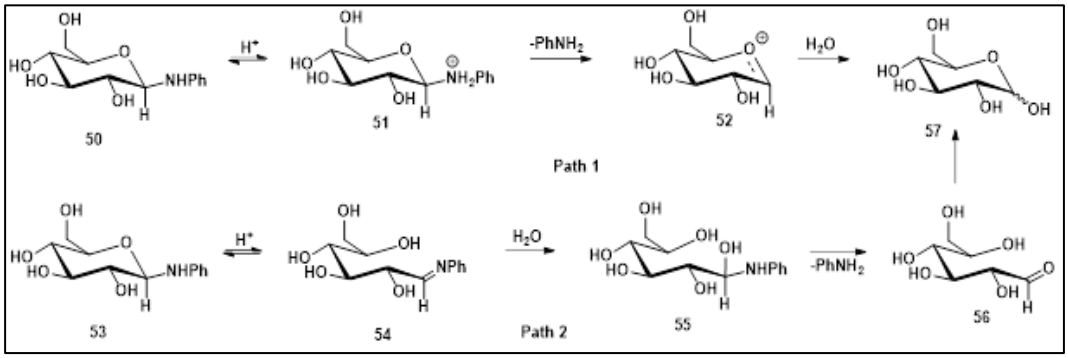


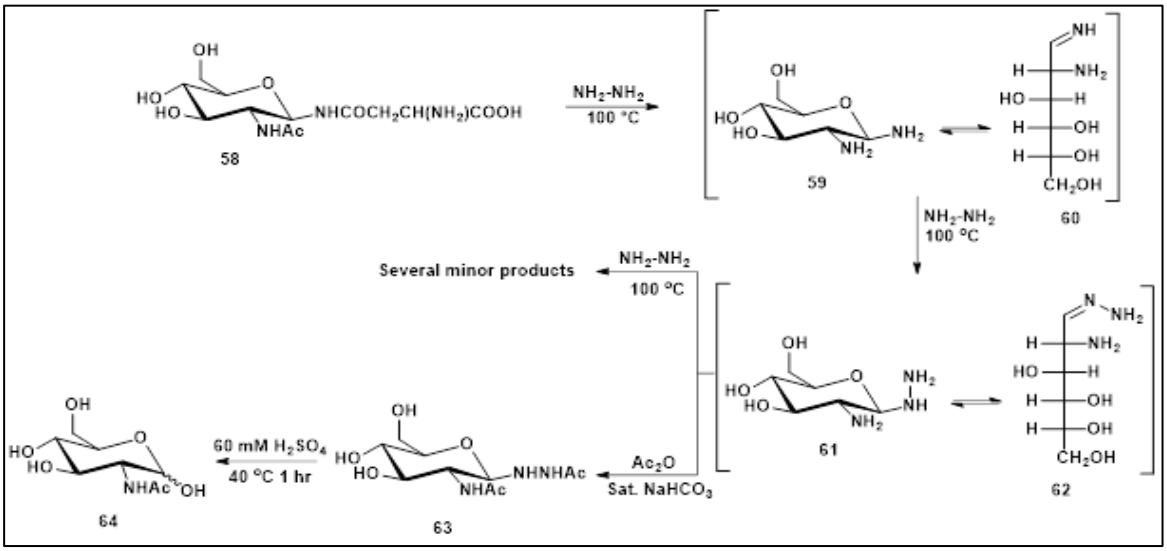
Figure 9. Transition state of solvolysis.

N-Glucosides are hydrolyzed by water under either acidic or basic conditions to yield glucose and amine derivatives.[71-72] The hydrolysis process involves a rapid interconversion of α- and β-anomeric forms, which was monitored through changes in optical rotation and the concentration of free amine (**Scheme 3**). It was proposed that the hydrolysis may proceed *via* cyclic (Path 1) or an acyclic Schiff base form (Path 2) under acidic conditions. Capon *et al.* conducted experiments to determine the preferred mechanism by introducing various substituents and observing their impact on the reaction rate.[73] These studies supported the progress of hydrolysis process *via* path 2.



Scheme 3. Hydrolysis pathway for *N*-glucopyranoside.

Hydrazinolysis is used to isolate the sugar part of glycoproteins during structural analysis of the latter. The released glycan can be easily transferred into the desired products like fluorescence tagging etc.[74-75] Williams and his group have studied the hydrogenolysis of 1-*N*-acetyl and 1-*N*-(L-β-aspartyl) derivatives of 2-acetamido-2-deoxy-β-D-glucopyranosylamine.[76-77] Hydrazinolysis of both the compounds yielded 2-amino-2-deoxy-D-glucose hydrazine as one of the products, along with glycosylhydrazide plus 4-amino-3,5-dimethyl-1,2,4-triazole and L-aspartic acid 4-hydrazide plus 2-amino-2-deoxy-D-glucose from 1-*N*-acetyl derivative and 1-*N*-(*L*-β-aspartyl) derivative respectively. Further, they reported the Wolff-Kishner reduction and osazone formation using hydrazine derivative. Bendiak *et al.* have reported the hydrogenolysis of 2-acetamido-1-*N*-(L-aspart-4-oyl)-2-deoxy-β-D-glucopyranosylamine (**58**) yielding **64** as one of the product (**Scheme 4**).[78]



Scheme 4. Hydrogenolysis of **58**.

5. Metal Complexes of Glucopyranosylamine-derived Ligands

Saccharide and metal ions co-exist in the biological system and controls several enzymatic processes,[79-80] which provokes the researchers to develop the structural and function analogue of such system. *In vitro* metal–saccharide interactions are known since about last two centuries as one of the reports on adduct of D-glucose with NaCl was reported

in 1825 by Calloud.[81] Several reports are available on metal saccharide (natural as well as modified) interactions, however literature on metal complexes of glucopyranosylamine derived ligands are limited. F. Micheel and A. Klemer synthesized sodium complexes of *N*-glycosides containing glucose and amino acids by *in situ* mixing of sugar, amino acid and sodium bicarbonate under mild basic condition (pH 7–8).[82] Later Weitzel *et al.* reacted metal (Mg(II), Ca(II), Co(II), Cu(II) and Zn(II)) complexes of amino acids with D-glucose to produce the metal ion bound *N*-glucosylamines.[83] Yano and co-worker have condensed the aldoses and ketoses with Cu(II), Ni(II), Co(III), and Mn(II) complexes of ethylenediamine (en) or its derivatives to prepare the corresponding metal bound *N*-glycosides.[84] Reaction of $[Ni(en \text{ or } tn)_3]^{2+}$ (tn = trimethylenediamine) with aldoses afforded octahedral complex and the same has been confirmed by single crystal X-ray diffraction studies of $[Ni(D\text{-}GlcN\text{-}en)_2]Br_2.4H_2O$ (Glc = glucose).[84] Both the nitrogen atoms of diamine and C2 hydroxyl group of sugar participated in the metal ion coordination.[85] They have also reported the reaction of *bis*(β-alaninato)nickel(II) complex with D-glucose, 4,6-*O*-benzylidene-D-glucose, etc. to isolate the octahedral Ni(II) complex.[86] Their other reactions include the *in situ* synthesis of glycosylamines and their interaction with metal salts to produce the glycosylamine-derived complexes.[87-89] Octahedral complexes of zinc $[Zn(D\text{-}GlcN\text{-}en)_2]^{2+}$ has been prepared by reacting D-glucosamine (D-GlcN) and ethylenediamine followed by metal salts.[90] Reactions of metal (Zn(II), Cu(II), Ni(II), salts with *in situ* generated *N*,*N*′-bis(D-glucopyranosyl)-1,4,7-triazacyclononane $[(D\text{-}Glc)_2\text{-}tacn]$ by reacting D-glucose and 1,4,7-triazacyclononane (tacn), afforded mononuclear divalent metal complexes. The synthesized Zn and Cu complexes were used as synthon for the preparation of homo and heterometallic complexes containing glycosylamines linkages.[91]

Gaucher *et al.* reacted D-glucose with diethylenetriamine to afford 1,3-*N*,*N*-di-β-D-glucopyranosyldiethylenetriamine, and the product interacted with $ZnCl_2$. The details of complex formation have been explored by mass spectrometry.[92] Cucciolito *et al.* have reported the synthesis of β-D-glucopyranosylamine-*N*-(2-pyridinylmethyl) derived Pt(II) complex **65** (**Figure 10**) and evaluated their cytotoxicity with respect to *cis*-platin on HeLa and MCF-7 cancer cells. The complex exhibited higher cytotoxicity on HeLa cells with respect to MCF-7 cells however the IC_{50} (Inhibitory Concentration 50) value is higher than the *cis*-platin.[93]

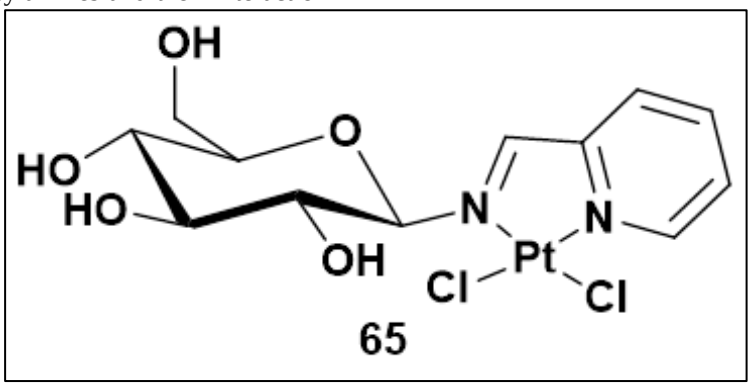
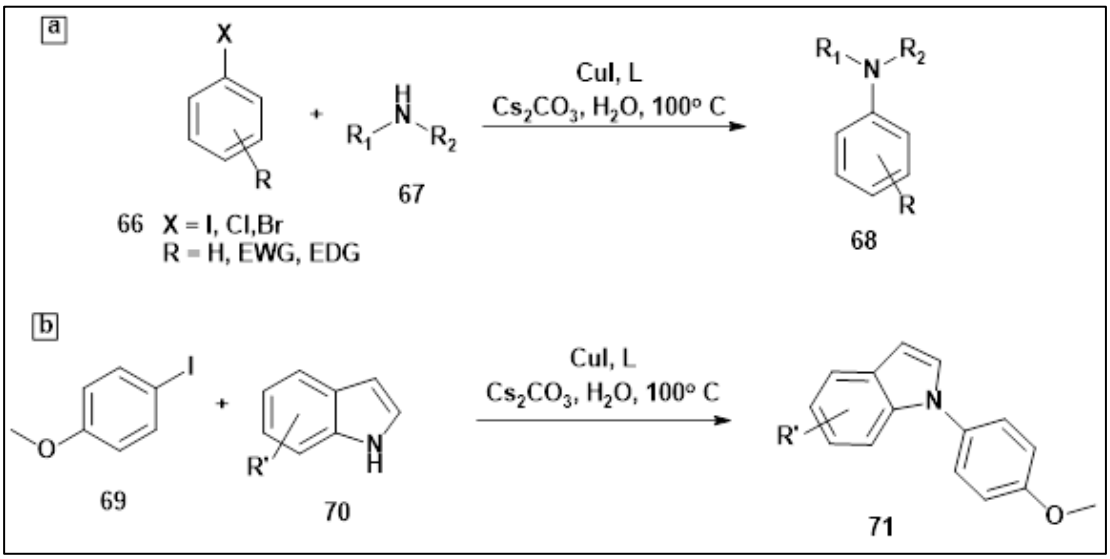


Figure 10. Structure of Pt(II) complex **65**.

Liu *et al.* have developed an efficient and greener route for the Ullman C-N coupling reaction catalyzed by *in situ* generated copper complex. The reaction vessel was charged with CuI and *N*-(2-hydroxyethyl)-β-D-glucopyranosylamine (L) as a ligand in 1:1 ratio respectively to catalyze the reaction (**Scheme 5**) and obtained the products in good yield.[94]



Scheme 5 (a) Coupling of aryl halides and nitrogen nucleophiles; (b) Reaction of indoles with 4-Iodoanisole

C. P. Rao's group had developed the anthranilic acid derived *N*-glycosylamine of 4,6-*O*-pretected glucose and explored their interaction with alkali (Li^+, Na^+, K^+), alkaline earth (Mg^{2+}, Ca^{2+}, Ba^{2+}) and transition metal (Zn^{2+}, Cd^{2+}, Hg^{2+}) ions.[36, 95] They proposed mono-anionic nature of *N*-glycosylamine ligand and the same was supported by crystal structure of it's potassium complex.[36] Further this group developed 4,6-*O*-pretected-*N*-glucosylamine derived Schiff base ligands and explored their interaction with various transition metal ions. Details of metallochemistry for this ligand till 2019 has already been reviewed by us under the title "Metal complexes of 4,6-*O*-ethylidene-β-D-glucopyranosylamine derivatives and their application in organic synthesis".[96] Latter Vimal *et al.*, reported the selective synthesis of sulfones using 4,6-*O*-ethylidine-*N*-(2-hydroxybenzylidene)-β-D-glucopyranosylamine **72** (**Figure 11a**) derived *cis*-dioxo molybdenum(VI) complex as catalyst and urea hydrogen peroxide as oxygen source.[97] Further Anuvasita *et al*. have synthesized the dinuclear molybdenum complex of *bis*(4,6-*O*-ethylidene-β-D-glucopyranosylamine)-1,4-dihydroxy-2,5-dibenzylidene for the sulfone synthesis with comparative low catalyst loading (1.2 mol %).[98] The interaction studies of **72** with lanthanide (III) ions has also been explored by Vimal *et al.*, for the first time and isolated the ytterbium complex. Further, the ytterbium complex ([Yb]) was used as catalyst in multicomponent synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones (**Scheme 6a**) with advantages over reaction time, catalyst loading and recyclability.[99] Recently, Santosh *et al.* have explored the metal ion (Na(I), Sn(II), Cr(III), Mn(II), Fe(III), Cu(II), Zn(II), Cd(II), Ag(I)) interactions with *N*-(2-hydroxynapthylidene)-L-leucienyl-4,6-*O*-ethylidene-β-D-glucopyranosylamine **77** (**Figure 11b**) at different pH range (4.2–9.1). During the studies, interaction of cupric acetate was immune to the pH variation. They also reported one-pot synthesis of [1,2-*a*] pyridines using 1:1 molar mixture of **77** and cupric acetate as catalyst (**Scheme 6b**). The reaction was performed at 80 °C under neat condition with 2 mol% of catalyst loading.[100]

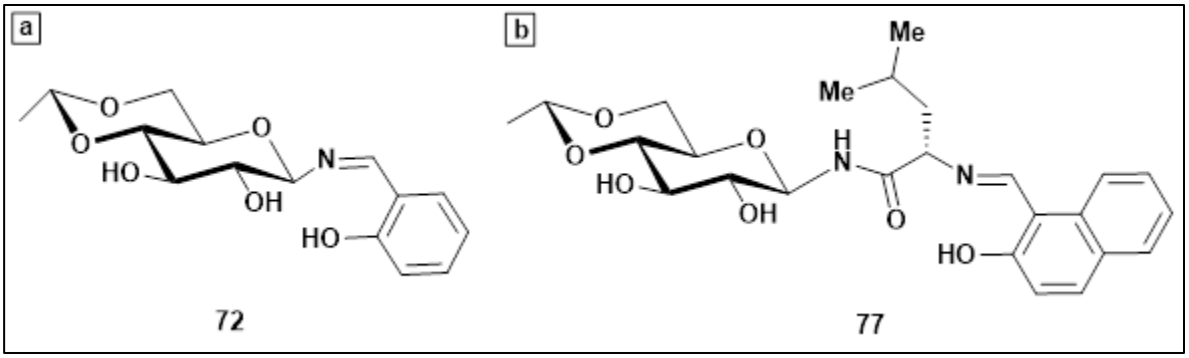
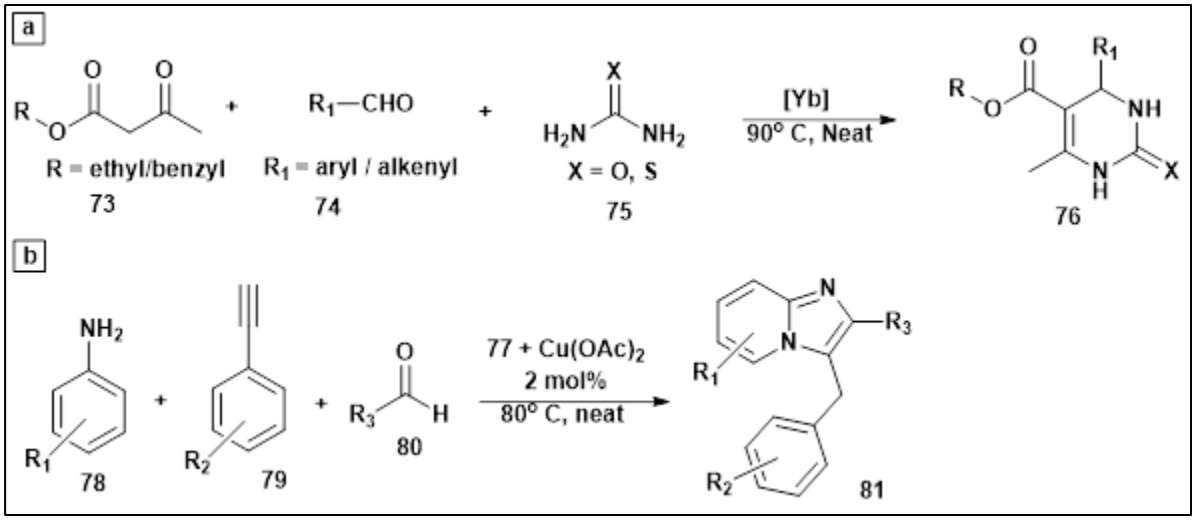


Figure 11. Structure of ligand (a) **72** and (b) **77**.



Scheme 6. Synthetic route of (a) 3,4-dihydropyrimidin-2(1H)-ones/thiones and (b) imidazo[1,2-*a*]pyridines.

6. *N*-Glucopyranosylamines as Receptor Molecules

Carbohydrates are associated with proteins, nucleic acids, lipids and metalloenzymes, which makes its occurrence massive in nature. Proteins attached to saccharides are commonly termed as glycoproteins, which performs various vital functions in the biological system. Jeroen *et al.* have prepared *N*-linked glycopeptides by coupling glucopyranosylamine with Boc- and Fmoc- protected amino acids. These monomeric units were used in the solid phase synthesis of short collagen mimics.[101] Kiran *et al.*, have reported the synthesis and crystal structure of alanyl-(4,6-*O*-ethylidene-β-D-glucopyranosylamine **82** (**Figure 12a**). The molecular structure of **82** reveals the presence of several hydrogen donor and acceptor sites in it, which have been used for the amino acid recognition. It selectively interacts with free as well as BSA (bovine serum albumin) bound tryptophan residue.[102] Along the same line, five amino acid appended 4,6-*O*-ethylidene-β-D-glucopyranosylamine derivatives **83-87** (**Figure 12b**) have been prepared and tested for the recognition of amino acids. Among these, four receptors containing phenylalanine derivative **83**, selectively interacts with cysteine while isoleucine **84**[103], alanine **85**, methionine **86** and valine **87** containing moieties interacts with aspartic acid.[104]

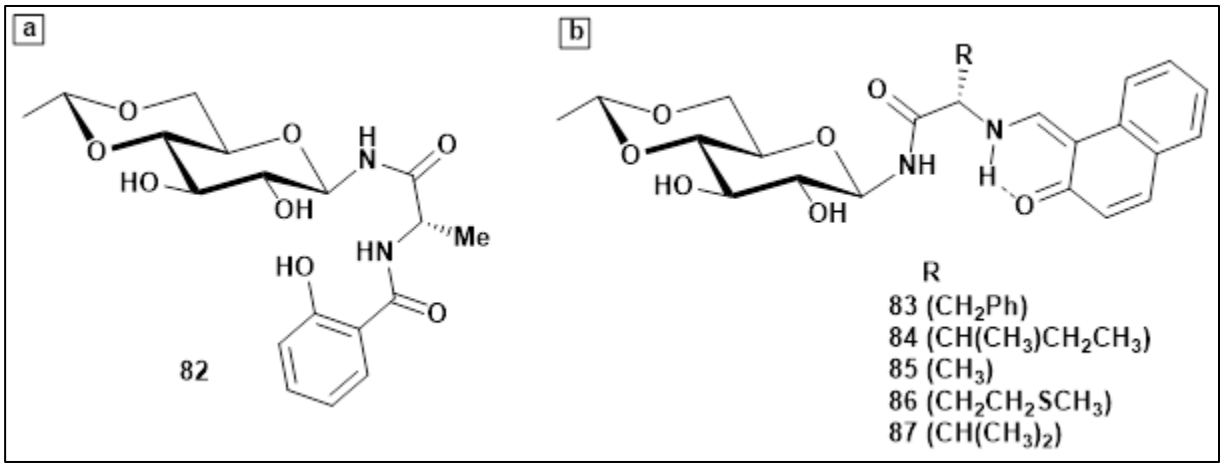


Figure 12. Structure of receptor(s) (a) **82** and (b) **83-87**

C. P. Rao's group have explored the anion sensing abilities of thiourea linked glucopyranosyl–anthraquinone conjugate receptor **88** (**Figure 13a**) and established its selectivity for F^- ion among 19 different anions.[105] Further they have developed triazole-linked glycoconjugate-based receptors **89-92** (**Figure 13b**) and explored their interaction with cyanide (CN^-) ion. Among the five receptors, **89** exhibited the highest enhancement in fluorescent intensity with CN^- ion.[106]

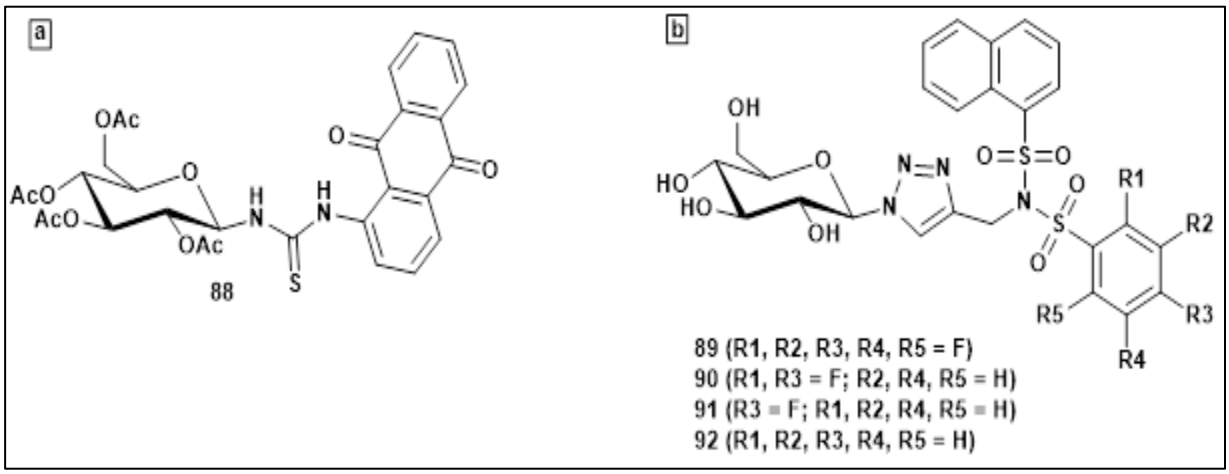


Figure 13. Structure of receptor molecules developed by C. P. Rao's group.

7. Glucopyranosylamine-derived Amphiphiles and Their Applications

Nanoporous materials have been extensively used in the capture, storage, and release of nanomaterials due to their inherent nano-scale voids. These materials also serve as scaffolds for catalysis, drug delivery, tissue engineering, molecular separation, and gas storage. Lipid nanotubes (LNTs) prepared using amphiphilic molecules were reported in 1984, which possess hollow cylindrical structures. Later, Shimizu and coworkers extensively explored the self-assembly (particularly for lipid nanotube synthesis with high axial ratios) of glucopyranosylamine-based amphiphilic molecules over three decades and the details are given below.

7.1 Unprotected glucopyranosylamine-based amphiphilic molecules.

A series of monounsaturated along with saturated and di unsaturated fatty acids having different positions of *cis*-double bond were condensed with β-D-glucopyranosylamine to result in the formation of glycolipids (**Figure 14a**). These molecules were explored for self-assembly and formation of most stable nano tube was noted with **93**.[107] The self-assembly of **93** in water forms LNTs having length of hundreds of micrometers, however mechanical stirring of lyophilized entity forms shorter LNTs (<10 μm).[108] The rolled-up bilayer self-assembly of **93** was also observed from cryogenic transmission electron microscopy.[109] The controlled outer diameters, inner diameters, and wall thickness were achieved by passing the aqueous suspension of **93** at 90 °C through a polycarbonate (PC) filter followed by filling of nanopores of anodic alumina membrane (AAM) filter with above filtrate.[110] In pursuit of enhanced functionality, the lyophilized LNTs were utilized in the synthesis of Au(0),[111] Ag(0),[112] and CdS[113] nanoparticles. Yang *et al.* have synthesized Au[114] nanowires, while Zhou *et al.* have developped CdS[115] nanowires on the LNT templet. The molecule **93** was further explored as nanocarriers for drug delivery and medical diagnosis systems.[116] The model system 8-anilinonaphthalene-1-sulfonate and Zn-phthalocyanine were encapsulated in **93** derived nanotube *via* the co-assembly technique.[116] Bhattacharya *et al.* explored the single-chain glycolipid-based amphiphiles as robust building blocks for artificial cells formation.[117] Ishikawa *et al.* have condensed saturated fatty acids with β-D-glucopyranosylamine and used the resultant amphiphiles (**Figure 14b**) in developing a variety of nanostructures. It was observed that the solvent variation can lead to the formation of sheets, nanotubes, and helical nano-coils *via* self-assembly.[118] Heating of nanotubes in water captures the dispersed fullerene (C60) inside it. Mixing of Au nanoparticles with fullerene containing nanotubes results in the deposition of Au on outer surface of nanotube, which releases back the C60 on irradiation with light.[118] Ding *et al.* have obtained the hybrid LNT from **98** and oleic acid, which were used in the fabrication of dopamine fibers. The dopamine incorporated LNTs were demonstrated to eliminate the HeLa cancer cells.[119]

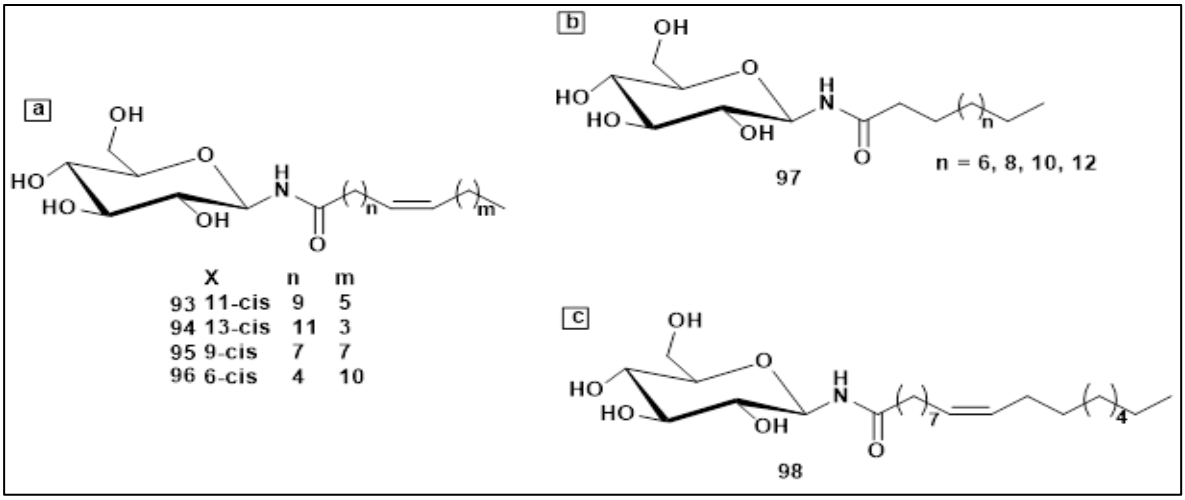


Figure 14. Structure of glucopyranosylamine-based amphiphilic molecules.

7.2 4,6-*O*-Protected glucopyranosylamine-based amphiphilic molecules.

Kameta *at. el.* has synthesized amphiphilic molecules by protecting 4- and 6- positions of glucopyranosylamine with boronic acid and further joining the amine with the fatty acids (**Figure 15**).

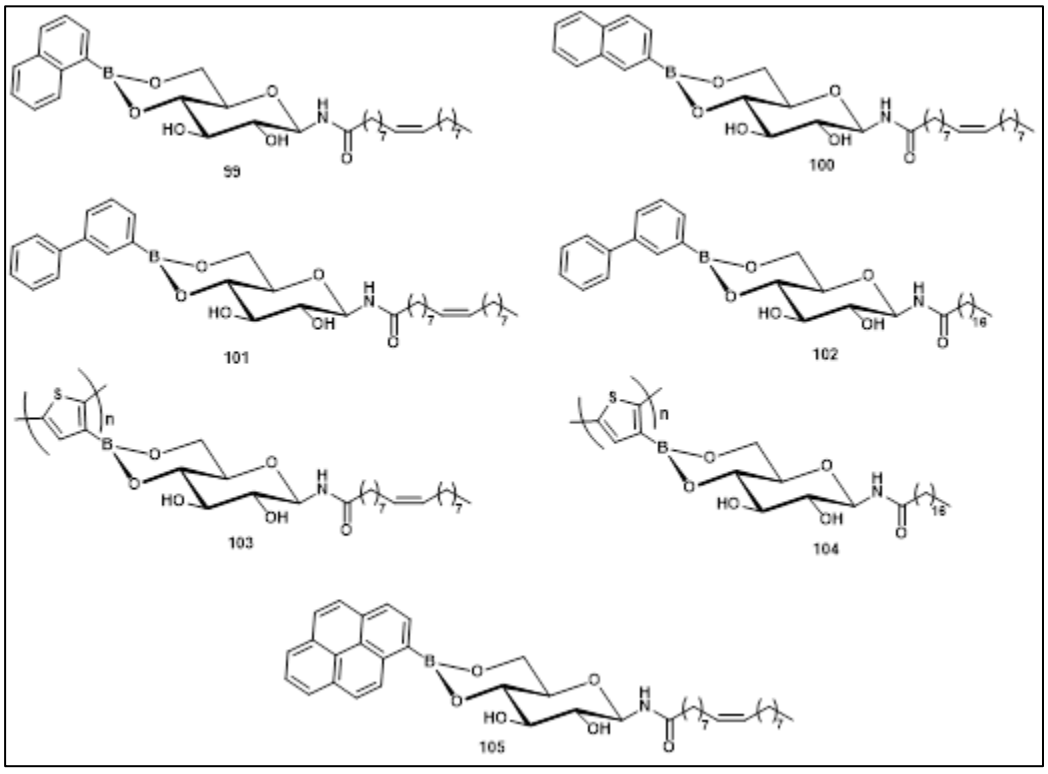


Figure 15. Structure of boronic acid-bearing glucopyranosylamine-based amphiphilic molecules.

99 and **100** were self-assembled into nanotapes and nanotubes, respectively, and were demonstrated as potential molecules for storing and transferring light energy.[120] Energy absorbed by packed naphthalene groups in the bilayer was efficiently released to an enclosed anthracene acceptor in the nanochannel. **101** and **102** encapsulates the Re(I)-bipyridine complex in the nanotube, which exhibit improved photoreduction activity for CO_2 reduction.[121] Polythiophene conjugated glycolipids **103** and **104** exhibit temperature-dependent circularly polarized luminescence.[122] Pyrene-based fluorescent glycolipids **105** exhibit morphological transformation from hollow vesicle to nanotube during chiral sensing of L-tryptophan and L-phenylalanine.[123]

Gel are viscoelastic materials consisting of low molecular weight gelator molecules. Non-ionic amphiphiles having carbohydrate head group serves as gelator molecule in pharmaceuticals, foods, cleaning agent etc. Structurally modified saccharides are recently being reported in the field of research as the hydroxyl groups can stabilize the gelator molecules *via* intermolecular hydrogen bonding.[124] Das *et al.* have synthesized six triaryl pyridine-based *N*-glucosylamine amphiphiles and studied their gelation property in aromatic and aliphatic solvents, and observed predominant gelation in aliphatic solvent with critical gelation concentration (CGC) of 0.5% w/v.[124] Later Das and coworker have reported the synthesis and morphological studies of 4,6-*O*-butylidene/ethylidene/benzylidene-β-D-glucopyranose gelator functionalized with azobenzene moieties.[125] 4,6-*O*-ethylidene-β-D-glucopyranosyl-3,4,5-tri-*O*- (alkyloxy)benzohydrazide gelators were synthesized by Kamalakannan *et al.* with CGC of 0.8% w/v in benzene. These gelators were used to gelate oil from biphasic oil-water medium and were also able to absorb dye with high efficiency.[126] Along the same line, Jenifer *et al.* reported photoresponsive alkyl chain containing azobenzene-sugar based gelator. The irradiation of UV light induces the *cis-trans* isomerization in azobenzene resulting in sol-gel transition. These gelators are highly effective in removing cationic dyes from polluted water.[12]

7.3 Symmetrical bola-amphiphiles

Masuda *et al.*, have reported the synthesis of bola-amphiphilic molecules having glucopyranosylamine at both ends.[128] Bola-amphiphiles with oligo-methylene chains (**106-115, Figure 16**) show self-assembly in water due to complementary and cooperative hydrogen-bonding networks of sugar hydroxy and amide groups.[129-134] It was observed that the chiral fibrous assemblies form when n is even, and it's odd value lead to the formation of platelets or amorphous solids. The bola-amphiphiles with a short-chain spacer (n = 6-8, 10) self-assembles in water to form gauche-including monolayered self-assembly, while medium and long-chain (n = 9 and > 11, 9) forms monolayered assemblies with all-*trans* oligo-methylene conformation.[128-133] The butadiynes were incorporated into the bola-amphiphile (**116**) as bridge to provide a potential candidate for the topochemical polymerization within the fiber monolayer lipid membranes (MLMs).[135]

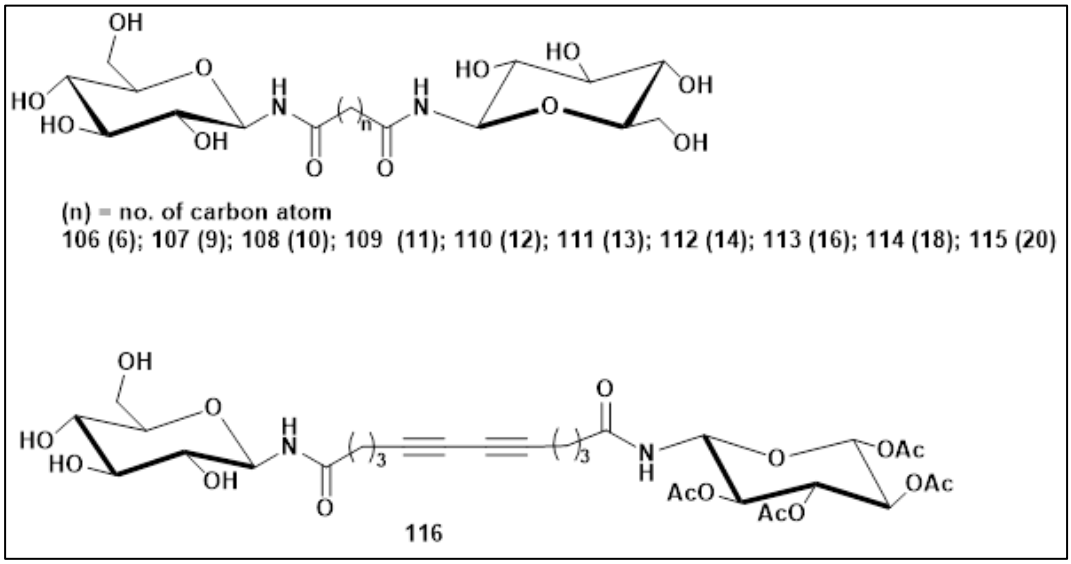


Figure 16. Structure of symmetrical bola-amphiphiles

7.4 Asymmetrical bola-amphiphiles.

Shimizu, Kameta, and Masuda are working on the bola-amphiphiles having two different hydrophilic moieties at the end. The molecules self-assemble in parallel or anti-parallel fashion, forming mono to multi-layer structures (**Figure 17**), providing more functionality based on molecular arrangement.[136] Several studies have been conducted by Kameta *et al.* on the self-assembly of unsymmetrical bola-amphiphiles. These molecules have amino acid,[137-142] carboxylate,[140] hydroxyl,[141] crown ether,[142] and Alexa Fluor 546 dye[143] as second head group. These molecules have been explored for encapsulation and release of enzymes, proteins, and other substances.

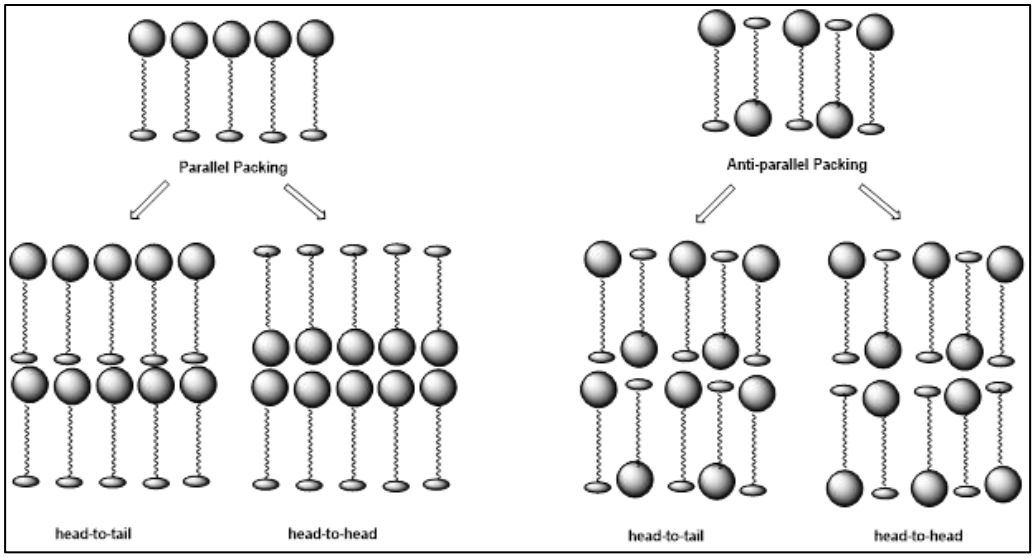


Figure 17. Patterns of self-assembly in asymmetrical bola-amphiphiles.

8. Biological Application of β-D-Glucopyranosylamine-based Compounds.

8.1 β-D-Glucopyranosyls as glycogen phosphorylase inhibitor

α-D-Glucose is a known physiological regulator for glycogen metabolism (inhibition constant (K_i) = 1.7mM) and inactivates the glycogen phosphorylation b (GPb), which reduces glycogen degradation to glucose.[144] Knowing these facts, researchers have developed several glucose analogues and tested their binding ability with GPb. The *N*-acyl derivatives of glucopyranosylamines have been proven to be the best inhibitory class of molecules. *N*-acetyl-β-D-glucopyranosylamine (NAG) act as a competitive inhibitor (K_i = 0.032 mM or 32 μM), where it tightly binds with the catalytic site of the GPb.[144] Watson *et al*. have tested a large number of glucose analogue by kinetic and crystallographic analysis to explore their potential as drug molecule.[145] Somsak *et al.* have reviewed several inhibitor molecules and glucopyranosylidene-spiro-hydantoin (**117**, **Figure 18**) was found as the most efficient inhibitor (K_i = 3-4 μM).[146] The replacement of the acetyl group by trifluoroacetyl group in NAG, resulted in another inhibitor *N*-trifluoroacetyl-β-D-glucopyranosylamine (NAF) with K_i = 75 μM.[147] The crystallographic studies reveal the similar GPb-NAG and GPb-NAF complex, however conformational change of protein residue in case of latter is noted.[147] Similarly replacement of acetyl group with azidoacetamido,[148] benzamido[149] and 4-phenyl-1,2,3-triazoleacetamido[149] moiety inhibit GPb with K_i = 48.7, 4.6 and 179 μM respectively. Later Watson *et al.* synthesized several glucopyranosylidene-spiro-hydantoin and β-D-glucopyranosylamine derivatives, however these molecules exhibited poor affinity in comparison to **96** due to the variation in binding interactions.[150] Hadjiloi *et al.* have synthesized oxalyl derivatives of β-D-glucopyranosylamine with good inhibition ability (Ki = 0.2–1.4 mM) than α-D-glucose.[151] Somsak and co-workers have prepared and investigated the inhibitory effect of 1-(β-D-glucopyranosyl)-4-substituted-1,2,3-triazoles (**118**)[152] and 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles (**119, Figure 18**)[153] on GPb, where latter compounds exhibited better inhibition ability than the former. Similarly, *N*-(β-D-glucopyranosyl)-1-substituted-1,2,3-triazole-4-carboxamides (**120**) and *N*-(β-D-glucopyranosyl)-3-substituted-isoxazole-5-carboxamide (**121**, **Figure 18**) offers the inhibition in low micromolar range.[154] Parmenopoulou *et al.* have screened a number of *N*-acyl-β-D-glucopyranosylamines by varying the R-group on acyl moiety. The best selected molecules from the screening were further assessed both *in vitro* and *ex vivo* for their inhibitory potency.[155] Fisher *et al.* have synthesized biphenyl-*N*-acyl-β-D-glucopyranosylamine with K_i = 9.7 μM, however the fluoro derivative of the same has less potency than the former (K_i = 56.1 μM).[156] Nóra *et al.* have synthesized several glycosyl biuret derivatives to investigate the effect of longer linker having *N*-acyl-N'-β-D-glucopyranosyl urea unit. The newly synthesized molecules offer optimal inhibition capacity.[157]

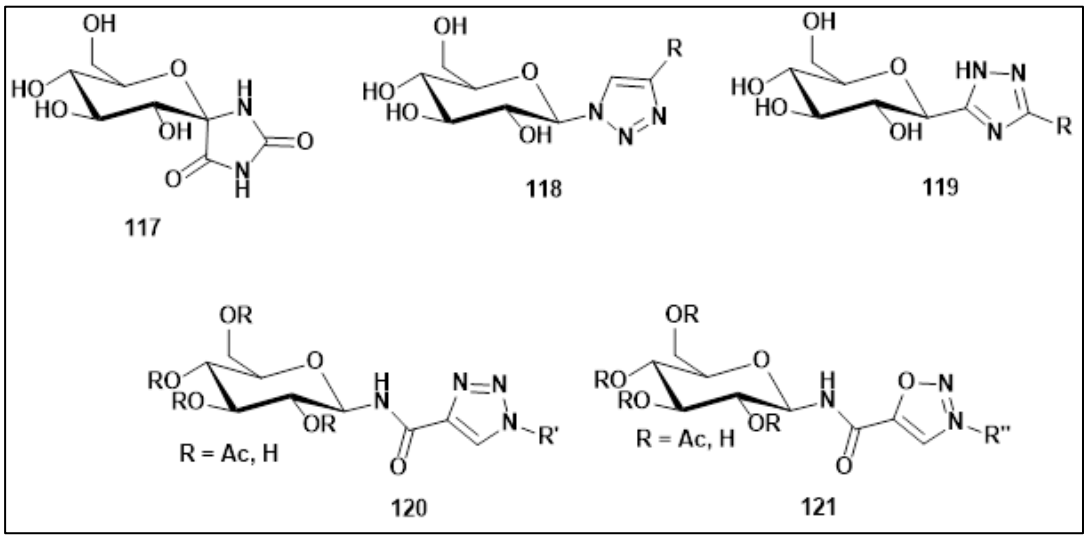


Figure 18. Structure of GPb inhibitors.

8.2. β-D-Glucopyranosyls as glycosidase inhibitor

Lai and Axelrod established the competitive inhibition of glycosidases by glycosylamines and reported 1-aminoglycosides as potent and selective inhibitors. D-glucopyranosylamine inhibits both α- and β-D-glucosidase, however it is more specific for β-glucosidase with K_i value 2.2 μM.[158] The β-glucosidases, isolated from sweet and bitter almonds show enhancement in inhibition by basic β-glucosyl derivatives than their neutral analogue.[159] Greenberg *et al.*, have explored the efficiency of *N*-C_n-glucosylamines (n = 6, 8,10,12,14,16 and 18, **Figure 19**) towards inhibition of human acid β-glucosidase enzyme. Among these inhibitors, best results were observed for glucosylamines with chain length; n = 12–18.[160] Kolarova *et al.* have investigated the inhibition activities of α-D-glucopyranosyl-β-D-glucopyranosylamine and di-β-D-glucopyranosylamine with inhibition constant (K_i) as 28 and 38 μM respectively, which is comparable with that of β-D-glucopyranosylamine (K_i = 24 μM). The inhibition constant of *N*-acetylated derivative of di-β-D-glucopyranosylamine was found to be 57 μM.[161]

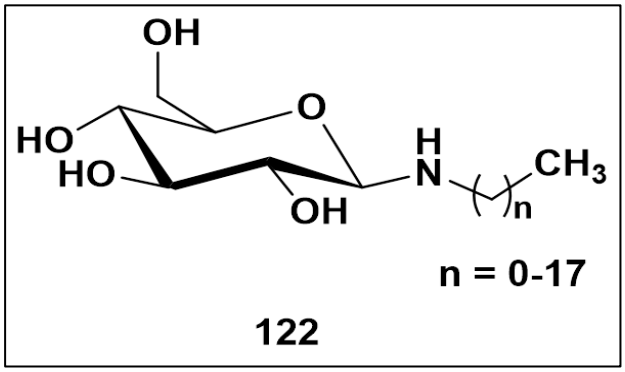


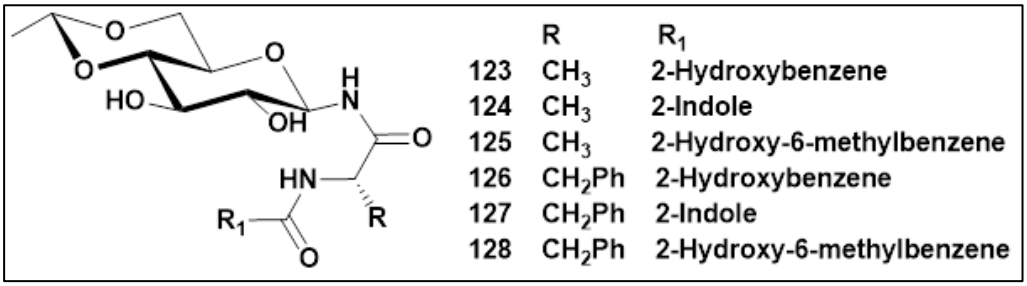
Figure 19. Structure of *N*-C_n-glucosylamines.

8.3. β-D-Glucopyranosyls as an antimicrobial agent

Glycosylamine derivatives have been tested for several pharmaceutical activities like antimicrobial, antifungal, antitumour agents etc. Hoever *et al.* have screened glycyrrhizin (GL) derivatives for inhibition of SARS-coronavirus (SARS-CoV) replication. It was observed that the GL conjugate of 2-acetamido-β-D-glucopyranosylamine has increased 10-fold anti-SARS-CoV activity as compared to GL.[162] Muhizi *et al.* reacted glucose with alkyl amine having different chain lengths and resultant glycosylamines were tested for antifungal activities. The extent of growth of *Coriolus versicolor* and *Poria placenta* were inhibited by increasing chain length.[163] These *N*-alkyl-β-D-glucosylamines have been also tested for their antimicrobial activity against *Fusarium proliferatum*, *Listeria innocua*, and *Salmonella typhimurium*. These compounds have

distinct biological activity, and their effectiveness increases with increasing alkyl chain length.[164] T. Muhizi has explored the antimicrobial activity of dimethylamino propyl glucosylamine. The compound showed antifungal activity against, *Fusarium oxysporum cubens* but was not effective to inhibit the growth the *Salmonella Typhimurium* and *Staphylococcus aureusagainst*.[165] Preparation of several *N*-glycosides has been reported by Shen *et al.*, out of which *N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl) benzo[*d*] oxazol-2-amine possess antibacterial activity against *Escherichia coli*.[166] Horvat *et al.*, have synthesized a series Leu- and Met-enkephalin analogues, where Gly^2 residue in Tyr-Gly-Gly-Phe-Leu/Met backbone was replaced with side-chain glucosylated D/L-aspartic or -glutamic acids. These glycosylated compounds moderately inhibit the growth of HeLa and SW 620 cancer cell lines.[167] Barros *et al.* have tagged glucopyranosylamine with mercaptoacetyl triglycine (MAG_3) and further labelled with technetium-99. This compound accumulates in tumour tissue, which makes it as a potential tumour diagnosis agent.[168] Gawolek *et al.* have synthesize several glycoconjugates from glucopyranosylamines and quinolones, which are cytotoxic against cancer cells at the micromolar level.[169] Parmenopoulou *et al.* have examined the cytotoxicity of *N*-acyl-β-D-glucopyranosylamines and their urea derivatives on CEM/L1210/HeLa tumor cell lines and DNA/RNA viruses. The *N*-acyl-β-D-glucopyranosylureas were proven to be more cytostatic than the corresponding amines.[170] A series of 4,6-*O*-ethylidene-β-D-glucopyranosylamine derived glycoconjugates (**Figure 20**) containing amino- and aromatic acids have been tested for their anti-inflammatory and analgesic activity. Anti-inflammatory studies were performed on Wistar rats whereas the analgesic studies were executed on Swiss Albino mice and all the tested molecule exhibited good activities.[171]

Nuran Kahriman and coworkers have synthesized sugar-glycoconjugates (methoxy substituted pyrimidine-*N*-glycosides) and their tetra-*O*-acetyl derivatives. The synthesized compounds were evaluated for antimicrobial and anticancer properties along with DNA/protein binding affinities.[172]



	R	R_1
123	CH_3	2-Hydroxybenzene
124	CH_3	2-Indole
125	CH_3	2-Hydroxy-6-methylbenzene
126	CH_2Ph	2-Hydroxybenzene
127	CH_2Ph	2-Indole
128	CH_2Ph	2-Hydroxy-6-methylbenzene

Figure 20. Structure of 4,6-*O*-ethylidene-β-D-glucopyranosylamine derived glycoconjugates.

Baig *et al.*, have synthesized amino acid derivatives of 4,6-*O*-ethylidene-β-D-glucopyranosylamine and explored their antibacterial activity through *in vitro* and *in silico* docking studies. The tryptophan and isoleucine derivatives unveiled best results against *E. coli* and *K. pneumoniae* bacterial strains respectively.[173] The amino-acid derived *N*-glycoconjugates were further condensed with salicylaldehyde and its derivatives to generate the corresponding Schiff bases. These derivatives exhibited fair amount of anti-bacterial activities, however only naphthylidene derivatives showed the antifungal activities.[174] Eight glycoconjugates containing quinoline moieties have been synthesized and evaluated for anti-inflammatory and anticancer activities. The compounds containing 6-fluoro-2-phenylquinoline-4-carboxamide and 2-(thiophen-2-yl)quinoline-4-carboxamide moieties show highest anti-inflammatory activity against human COX-2 enzyme and the latter one also exhibit maximum cytotoxicity against HeLa and human cervical cancer cell lines.[175]

A series of *N*-glycopeptides containing mefenamic acid were synthesized and their *in vitro* COX-2 inhibition activity has been explored by Vimal *et al.* All the molecules exhibited a fair amount of enzyme inhibition, and the best results was obtained for tryptophan derivative. The General Unrestricted Structure-Activity Relationships (GUSAR) software has been utilized to analyse the acute toxicity in rats which indicates least acute toxicity through oral modes of administration.[176]

9. Miscellaneous

Due to versatile use of *N*-glucopyranosylamine and it's derivatives, several groups have developed efficient synthetic routes of *N*-glycoconjugates. The 2-acetamido-1-*N*-(β-L-aspartyl)-2-deoxy-β-D-glucopyranosylamine residue **129** (**Figure 21**) is a fundamental component of natural glycoproteins like egg albumin, ovine submaxillary gland mucoprotein, human serum γ-globulin, etc. and possess antigenic properties. It holds a pivotal role in the comprehension of glycoprotein structural characteristics. To gain insights into the properties of

such carbohydrate-protein linkage, various research groups synthesized several derivatives of **129**, known as neoglycoproteins.[177-184] Jeanloz *et al.* synthesized multiple derivatives of glycopeptides containing 2-acetamido-1-*N*-(4-L-aspartyl)-2-deoxy-β-D-glucopyranosylamine residue .[184-191] Korytnyk and coworker have synthesized a range of *N*-substituted derivatives of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosylamine to explore their potential as inhibitors for the metabolism of cellular-membrane glycoconjugates.[192-193] Among these, fully acetylated derivatives exhibited notable growth inhibition of mouse mammary adenocarcinoma TA3, leukemia L-1210, and leukemia P-288 cells ranging from 1 to 0.01 mM concentration. Furthermore, alternative amino acids analogous such as alanyl, lysyl,[178] glycyl, alanyl, L-valyl, -glutamyl, seryl,[179] glutam-5-oyl,[181] asparagine,[194-196] have been employed in lieu of the aspartyl group. Likhosherstov *et al.* synthesized various *N*-haloacetyl-β-glycopyranosylamines of mono-, di- and oligosaccharides which were further utilized to prepare glycoconjugates of nitrogen-containing active molecules.[197-203] Loganathan and co-worker have utilized *N*-chloroacetyl-β-glycopyranosylamines to prepare *N*-(β-glycopyranosyl)azidoacetamides, mimetics of the widely distributed GlcNAc-Asn linkage in glycoproteins.[204-205]

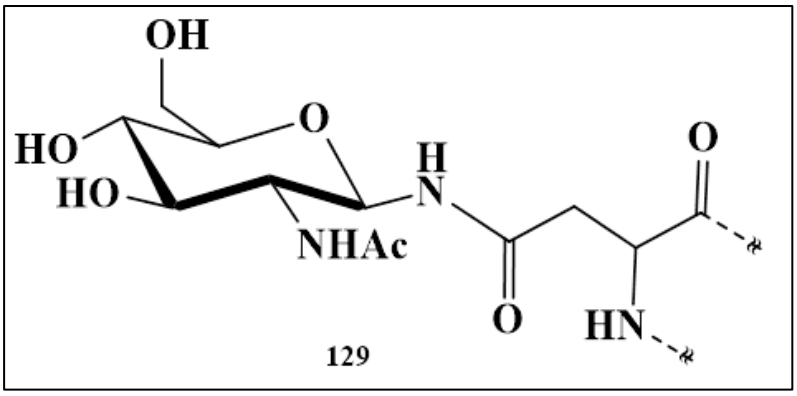


Figure 21. Structure of 2-acetamido-1-*N*-(β-L-aspartyl)-2-deoxy-β-D-glucopyranosylamine residue

Szczerek and Urbanski reacted D-glucopyranosylamine with 2-alkyl-2-nitropropane-1,3-diols and formaldehyde to synthesize 5-alkyl-3-(β-D-glucopyranosyl)-5-nitrotetrahydro-1,3-oxazines.[206] Kuwahara *et al.* have reported the formation of *N*-(2-amino-1,2-dicyanoethylenyl)-β-D-glucopyranosylamine by fungal degradation of diaminomaleonitrile in D-glucose medium.[207] Weng *et al.* have prepared *O*-unprotected glycosyltriazenes, where 1-anthraquinone-1-diazonium hydrogensulfate were coupled with β-glycopyranosylamines. The Triazene products are stable due to intramolecular hydrogen bond between NH proton and anthraquinone carbonyl oxygen atom.[208] Shin and co-worker developed a simple and effective synthetic route for *N*-acryloyl derivatives of 2-acetamido-2-deoxy-β-D-glucopyranosylamine. Their synthesis includes the formation of 2-acetamido-*N*-acryloyl-2-deoxy-β-D-glucopyranosylamine and 2-acetamido-*N*-(*N*-acryloylglycinyl)-2-deoxy-β-D-glucopyranosylamine starting from 2-acetamido-2-deoxy-D-glucopyranose.[209]

Glycoproteins and glycopeptides play a key role in the biological system, which makes glycoconjugates a desired scaffold for drug design. Burger and co-worker reported a new approach for the synthesis of glycopeptides. Here malic, citramalic, and thiomalic acid, were protected by hexafluoroacetone, and the resultant molecules were reacted with *O*-protected glucopyranosylamine. The products were further reacted with amino acid or dipeptides to generate a series of *N*-glycoconjugates.[210] Feliciana *et al.* have coupled the β-D-glucopyranosylamine with the aspartic acid under microwave irradiations to form the glycopeptides.[211] Maria and Alessandro have synthesized *N*-glycosyl-Asp-urea conjugates by three-component domino reaction between carbodiimides, fumaric acid monoesters and glycosylamines.[212] Alexandre *et al.* reported the stereoselective copper-catalyzed coupling of glucopyranosylamine with functionalized aryl boronic acid at room temperature to produce variety of aryl *N*-glycosides.[213]

10. Conclusion

N-Glucopyranosylamine-derived molecules have been explored by researchers from chemistry, biology and pharmaceutical sciences due to their versatile nature. Their research outcome has been elaborated under the subheadings like synthesis, stability and application. Synthesis section includes the details of synthetic methodologies and varieties of molecules developed. The particulars of studies on anomerization and consequences of this process has

been summarized under stability. Glucopyranosylamines are majorly found in β-anomeric form, however methods have been developed for selective synthesis of α-anomer. *N*-Glucoconjugates have been used in metal chelation, molecular recognition, molecular aggregation, medicine and drug delivery systems.

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Conflicts of interest

The authors have no conflict of interest to declare.

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