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A convenient synthesis of novel pyranosyl homo-C-nucleosides and their antidiabetic activities

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ABSTRACT

A series of pyranosyl homo-C-nucleosides have been synthesized by reaction of butenonyl C-glycosides (**5a**–**5j**, and **8**) and cyanoacetamide in presence of *t*-BuOK followed by further modifications. The reaction proceeds by Michael addition of cyanoacetamide to the butenonyl C-glycosides and subsequent dehydrative cyclization and oxidative aromatization to give glycosylmethyl pyridones (**6a**–**6j**, **7a**–**7j**, **9,** and **10**). The glycosylmethyl pyridones (**6a**–**6e**) on reaction with $POCl_3$ under reflux gave respective glycosylmethyl pyridines (**11a**–**11e** and **12a**–**12e**) in good yields. The synthesized compounds were screened for their in vitro α-glucosidase, glucose-6-phosphatase and glycogen phosphorylase inhibitory activities. One of the pyridylmethyl homo-C-nucleoside, compound **11d**, displayed 52% inhibition of glucose-6-phosphatase as compared to the standard drug sodium orthovanadate while compound **12a** showed a significant antihyperglycemic effect of 17.1% in the diabetic rats as compared to the standard drug metformin.

1. Introduction

The synthetic interest in nucleoside analogs is due to their capability to interfere with functioning of enzymes, which renders them antiviral, anticancer, antibacterial, insecticidal, fungicidal, and herbicidal, among other known biological activities. The demand and utility of nucleosides and their analogs is continuously increasing due to the spread of HIV, hepatitis B, herpes simplex and other viruses.[1–6] The homo-C-nucleosides, which have a $–CH_2–$ linker between the sugar and heterocyclic moiety are also of great biological significance and are potent chemotherapeutic agents or enzyme inhibitors.[7,8] Further, among the α- and β-anomeric nucleosides, the latter have extensively been studied due to their natural occurrence and numerous biological activities, while the α-nucleosides have received little attention.[9–11]

Diabetes mellitus commonly known as diabetes is a group of metabolic diseases characterized by abnormally high levels of plasma glucose. Inhibition of glycosidases, glucose-6-phosphatase and glycogen phosphorylase are known to reduce the hyperglycemia. Very recently renal SGLT2 (sodium-dependant glucose co-transporter), located on the surface of the epithelial cells and lining the S1 segment of the proximal tubule, is reported to facilitate >90% of renal glucose re-absorption.[12,13] Selective inhibition of SGLT2, therefore, results in preventing glucose re-absorption, which may lead to new antidiabetic drugs with no gastrointestinal side effects. Nucleoside analogues and pyridine-based compounds are known to inhibit the above glycosidases and result in limiting hyperglycemia. Several aryl C-glycosides (dapagliflozin, sergliflozin, LX-4211) and many other heteroaromatic-C-glycosides such as compound **4** are potent SGLT2 inhibitors[13–15] (Fig. 1) and possess very good antidiabetic activities in vivo. The dapagliflozin is in phase III clinical trial for the treatment of diabetes.[14] Further, certain nucleosides and pyridine derivatives are known to inhibit hepatic glycosidases and possess a hypoglycemic effect.[16,17]

A number of methods exist in literature toward the synthesis of aryl β-C-glycosides[18–21] including those clinical candidates for the treatment of diabetes. In general, methods known so far, are based on nucleophilic attack at the anomeric carbon of the sugar, the glycosylidene carbene formation,[22–24] or Wittig-type reaction[25] or substitution of the hydroxyl group at the anomeric carbon with halogen and subsequent reactions such as Reformatsky,[26] Grignard,[27] or free-radical reactions.[28] The methods adopted for the synthesis of antidiabetic aryl β-C-glycosides involve the use of BuLi and restricted reaction conditions. Most of these methods of β-C-glycoside syntheses require a metal-based catalyst and inert atmosphere for successful completion of the reaction. Keeping in mind the above facts and in continuation of our ongoing studies toward the synthesis of β-C-glycosides[29–31] as new antidiabetic agents, we

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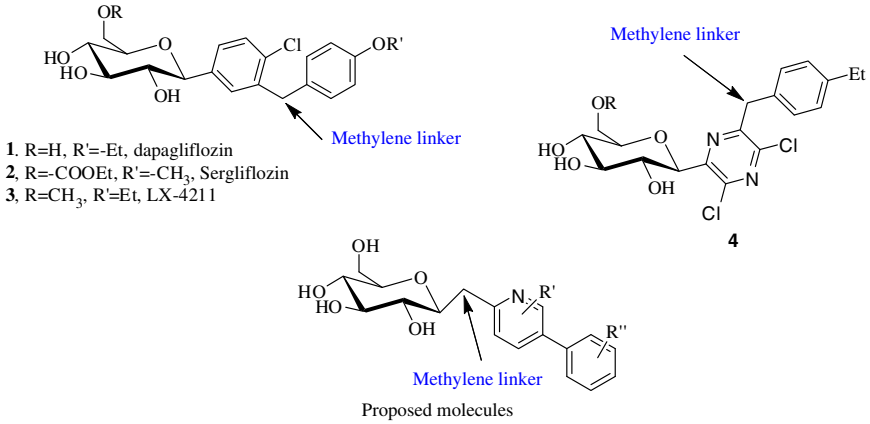


Figure 1. Antidiabetic β-C-glucosides **1–4** in clinical trial and our designed molecules.

were interested in the synthesis of heteroaryl β-C-glycosides as homo-C-nucleoside analogs and evaluating their antidibetic activities.

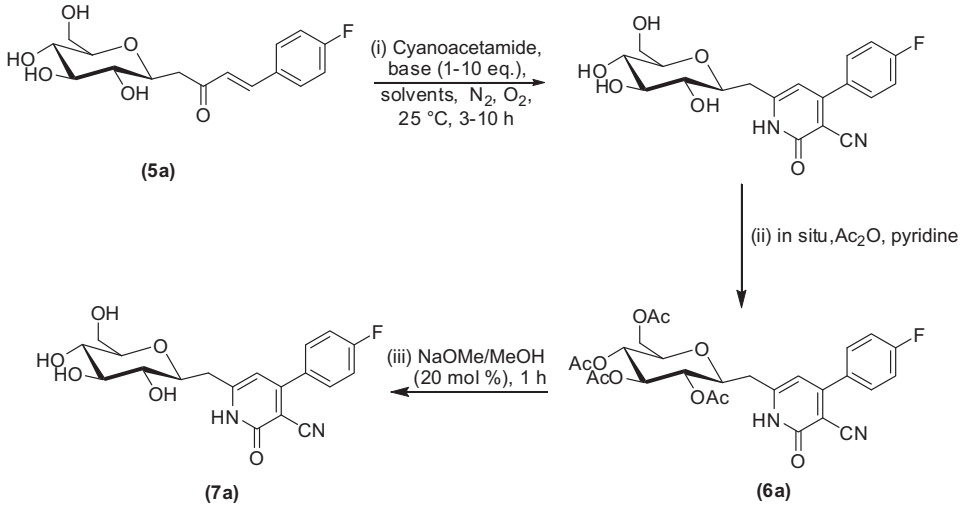
Our method of pyranosyl homo-β-C-nucleoside synthesis involves reaction of the butenonyl C-glycosides with cyanoacetamide followed by further modification of the intermediates. The reaction proceeds by 1,4-conjugate addition (Michael addition) of cyanoacetamide on to the butenonyl C-glycoside to give an intermediate which on dehydrative cyclization and subsequent oxidative aromatization offers the glycopyranosyl methyl pyridine. The latter on refluxing with $POCl_3$ gives the respective pyridylmethyl glycosides. The compounds are evaluated for their antidiabetic potential in vitro. The method adopted in the synthesis is quite simple, eco-friendly, and economical as it involves easily available sugars and reagents.

2. Results and discussion

2.1. Chemistry

The starting butenonyl C-glycosides (**5a–5j**) were prepared from commercially available D-glucose following our method and earlier reported protocols.[29–32] To optimize the reaction conditions, the reaction of 1 equivalent of (*E*)-1-(β-D-glucopyranosyl)-4-(4′-fluorophenyl)-but-3-en-2-one (**5a**) with cyanoacetamide (1–10 equiv) in different organic solvents, under the influence of various inorganic and organic bases, and under an N_2 atmosphere at ambient temperature for 30 min (until the disappearance of starting butenoyl C-glycoside) was carried out. The reaction mixture was brought under the influence of an O_2 atmosphere to carry out oxidative aromatization. The reaction mixture was subsequently acetylated with Ac_2O/pyridine (Scheme 1, Table 1) in order to facilitate the isolation of the pure product by column chromatography. Four equivalents of *t*-BuOK in DMSO at ambient temperature proved to be the most optimum reaction conditions (entry 6) followed by in situ acetylation of the reaction mixture to give the desired compound 3-cyano-4-(4′-fluorophenyl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridone (**6a**) in 53% yield (Table 1). It is appropriate to mention here that many other minor products observed on TLC plate could not be isolated in pure forms despite our several attempts.

The structure of 3-cyano-4-(4′-fluorophenyl)-6-[(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]pyridone (**6a**) was established on the basis of its spectroscopic data and analysis. The IR spectrum exhibited absorption bands at 3467 cm^{-1}, 1662 cm^{-1} and 1753 cm^{-1} indicating the presence of NH and N–C=O groups of the pyridone ring and carbonyl of the sugar acetyl groups, while an absorption band at 2227 cm^{-1} indicated the presence of cyano (CN) group. ESIMS of the compound displayed *m/z* 559 $[M+H]^+$ peak. In the ^1H NMR spectrum the exchangeable



Scheme 1. Optimization of reaction conditions with compound **5a** and cyanoacetamide.