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Synthesis of 1,2,3-triazole glycoconjugates as inhibitors of α-glucosidases

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ABSTRACT

Ten new 1,2,3-triazole glycoconjugates were synthesized from D-glucose and evaluated in in vitro assays for their ability to inhibit the enzyme α-glucosidase. Most of the compounds had low activity or were inactive when compared with acarbose. However, the derivative 1,2-*O*-isopropylidene-3-phenyl-5-(4-phenyl-1*H*-1,2,3-triazole-1-yl)-α-D-ribofuranose (**19i**) possessed activity comparable with the standard drug. The influence of the phenyl group on carbon 3 of the carbohydrate framework is discussed.

1. Introduction

A glycosidic bond is a covalent chemical bond between the anomeric carbon atom of a saccharide and some other group or molecule. Many polysaccharides are formed from the union of monosaccharides by α- or β-glycosidic bonds. During the digestion process, these bonds are hydrolyzed by specific glycosidase enzymes that liberate the carbohydrate units as nutrients.[1] For instance, α-amylase enzymes are produced in the digestive system to break down the α-glycosidic bonds of starch. Several glycosidase enzymes are involved in important biological processes,[2] such as intestinal digestion and the lysosomal catabolism of glycoconjugates. Additionally, these enzymes are involved in virus production[3,4] and cancer metastasis[5–7] and are targets for anti-hyperglycemic pharmacological agents. In this regard, digestive α-glucosidases control rapid increases in blood glucose and therefore are therapeutically useful for the treatment of metabolic diseases such as diabetes mellitus.[8]

Many organisms have endogenous inhibitors that control the activity of glycosidases and glycosyl transferases. For instance, nojirimycin (**1**) and deoxynojirimycin (**2**) are potent inhibitors for α- and β-glucosidases and are produced by several natural sources. Since the discovery of these compounds, several other glycosidase inhibitors have been isolated from plants and microorganisms.[9] The search for α-glucosidase inhibitors led to the isolation of acarbose (**3**), marketed as Glucobay® and Precose, from the Actinoplanes strain SE 50 and is used as a potent sucrase inhibitor (Fig. 1).[10] Acarbose consists of a polyhydroxylated aminocyclohexene derivative (valienamine) that is linked via its nitrogen atom to 6-deoxyglucose, which is α-(1→4)-linked to a maltose moiety (Fig. 1). This compound inhibits pig intestinal sucrase with an IC_{50} of 0.5 mM.[11] After many clinical investigations, acarbose was introduced in the market in 1990 for the treatment of type 2 diabetes mellitus.[7] The inhibition of pancreatic α-amylase and intestinal α-glucosidases has demonstrated great value in the control of blood glucose levels by slowing down the starch digestion rate.[12–16] The strong inhibition of human amylases by acarbose (IC_{50} 108.8 ± 12.3 μM) is attributed both to the partial planarity of the valienamine ring and to the presence of strong electrostatic interactions between the carboxyl groups at the active site and the protonated nitrogen atom of the inhibitor.

Polysubstituted five-membered azaheterocycles have been described as potent glycosidase inhibitors. These heterocycles mimic the sugars moieties, and notable structural scaffolds include pyrrole-, imidazole-,[17,18] [1,2,3]-triazole-[19–24], and tetrazolo-glycoderivatives.[25,26]

The importance of triazolic compounds is of particular interest for medicinal chemistry, and many of them have been employed as pharmaceutically active compounds or as prototypes for potential drugs. In this regard, [1,2,3]-triazoles have gained increasing attention due to the ease of their incorporation into molecules via 'click' chemistry.[27,28] These heterocycles can actively participate in hydrogen bonding and dipole–dipole interactions due to their strong dipole moments. Additionally, they are extremely stable against hydrolysis and oxidative/reductive conditions. They are

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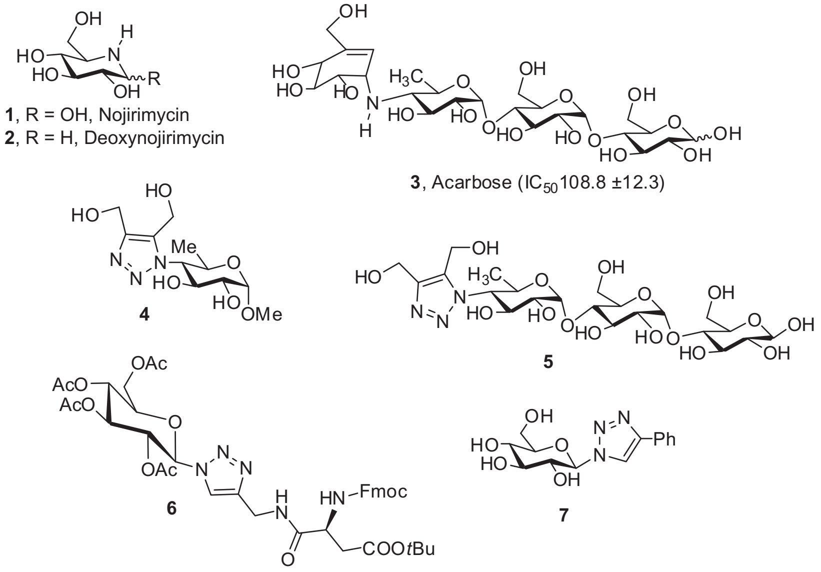

Figure 1. Some examples of α-glucosidases inhibitors.

significantly active against various biological targets[29] such as tuberculostatic,[12,30] antiplatelet agents,[31] dopamine D_2 receptors related to schizophrenia,[32] and anticonvulsant,[33] anti-inflammatory,[34,35] anti-allergic,[36–39] antiviral,[40–43] and antimicrobial agents.[19,44–47] Several 1,2,3-triazoles are described in the literature as glycoconjugates for the inhibition of α-glucosidases (**4–7**, Fig. 1).[19–24]

Compounds with triazole as the core system have promising α-glucosidase inhibition activity. Our research group recently reported the synthesis of 1,2,3-glycotriazole derivatives, and two of them displayed a high degree of inhibition of the α-glucosidase enzyme.[48] Notably, β-D-ribosyl triazoles **8** and **9** showed the greatest activity (Fig. 2). In a continuing effort to find new glycotriazole analogues and to better understand the relationship between structural changes and the activities of these substances, we investigated structural changes in these compounds by introducing a phenyl group at the C-3 carbon of the carbohydrate and moving the isopropylidene moiety to the C-1 and the C-2 positions as indicated in Figure 2.

2. Results

Melting points were observed on a Fischer–Jones apparatus and are uncorrected. Analytical grade solvents were used.[49] Dioxane was distilled before use. Reagents were purchased from Aldrich or Acros Chemical Co. Column chromatography was performed on silica gels (Acros Organics 0.035–0.070 mm, pore diameter 6 nm). Yields refer to the chromatographically and spectroscopically homogeneous materials. Reactions were monitored by thin layer chromatography (TLC) and were carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an ethanolic solution of sulfuric acid. Infrared spectra were recorded on a Perkin–Elmer FT-IR Spectrum One spectrophotometer was calibrated relative to the 1601.8 cm^{-1} absorbance of polystyrene. Optical rotation measurements were obtained using an Acatec PDA 9300 polarimeter. NMR spectra were recorded on a Varian Unity Plus VXR (300 MHz) instrument in DMSO-d_6 and $CDCl_3$ solutions, and tetramethylsilane was used as the internal standard ($\delta = 0$ ppm). Elemental analysis was used to determine the purity of the compounds for which biological data were determined.

To obtain the triazoles planned in this work, we followed the synthetic route from D-glucose (**10**) as described in Scheme 1. The route consisted of a series of simple reactions involving the initial formation of a diacetonide (**11**),[50] followed by the oxidation of the hydroxyl group at the C-3 position and the addition of the phenyl group to the carbonyl, which occurs selectively at the *si* face,[51] producing **12**. The selective removal of the isopropylidene group

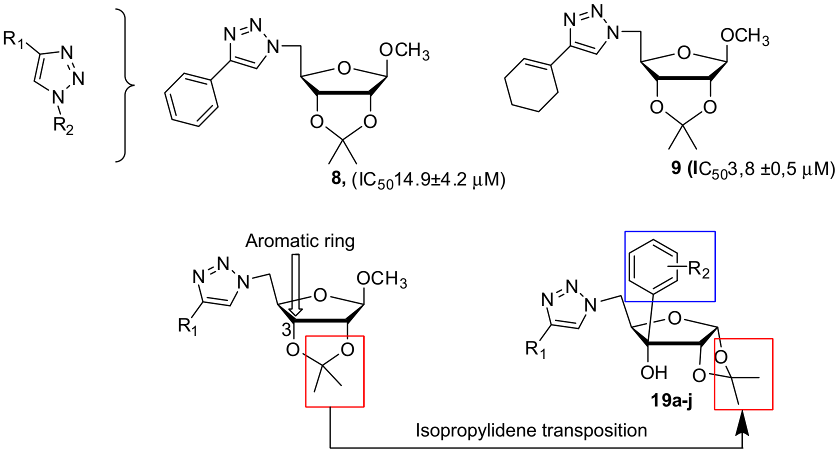

Figure 2. Planning concepts for the synthesis of glycotriazoles **19a–j**.