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Synthesis of rapamycin glycoconjugates via a CuAAC-based approach

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ABSTRACT

The conversion of the C40 secondary hydroxyl group of rapamycin into the azido group was followed by copper catalyzed cycloaddition of the resulting azido-rapamcin with various unprotected propargyl *O*- and *S*-glycosides and a *C*-ethynyl derivative. This approach furnished a collection of triazole-bridged rapamycin glycoconjugates (14 examples) in 44–83% isolated yield.

It is well established that glycosidic residues appended to pharmaceutically important natural products can influence their key pharmacological and pharmacokinetic properties.[1] Quite significant is the case of vancomycin whose glycosylated analogs are known to display an improved activity against vancomycin-resistance bacteria.[2] Thus, while several glycosylated natural products of pharmaceutical importance are known,[1c] there is precedent for improving non-glycosylated therapeutics by glycoconjugation, including colchicine,[3] mitomycin,[4] podophyllotoxin,[5] isophosphoramide mustards,[6] or taxol.[7] Rapamycin **1** (Fig. 1), isolated four decades ago from a culture of *Streptomyces hygroscopicus* NRRL 5491, obtained from a soil sample collected on Easter Island (Rapa Nui),[8] has been the target of similar efforts. In fact, a patent was reported by Abel et al. describing the synthesis of rapamycin glycoconjugates in which the sugar residues were attached through an ester linkage to either the C40 or C28 of the macrolide.[9] Although mixtures of glycoconjugates appeared to have been formed, their administration demonstrated altered pharmacokinetic profiles and reduced toxicities. Thus, although rapamycin **1** itself is well characterized as a potent immunosuppressant and also as an antiproliferative and antitumor agent,[10] the modification of its poor physiochemical properties by glycoconjugation is a topic of great interest. We report below an approach toward the introduction of glycosyl residues in **1** by using the copper-catalyzed cycloaddition between a C40 azido derivative of **1** and alkynyl *O*-, *S*-, and *C*-glycosides. We settled on the use of the most popular click reaction, that is the Cu-catalyzed azide–alkyne cycloaddition (CuAAC),[11] for two main reasons. First, this approach would lead to glycoconjugates having the sugar and the aglycone moieties connected through the triazole ring. We envisaged that the triazole ring could serve not only as a highly stable linker but could also

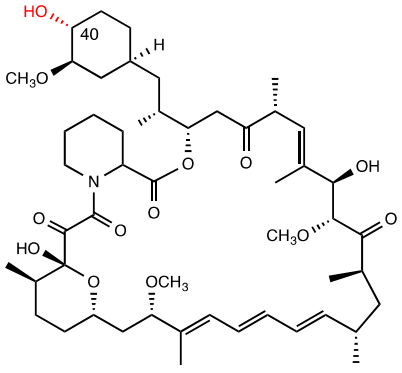

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Figure 1. Rapamycin.

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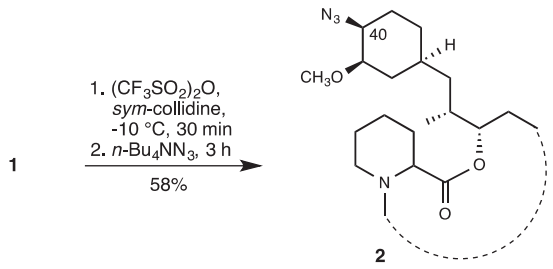


Scheme 1. New conditions for the preparation of the azido-rapamycin **2**.

induce some beneficial physicochemical properties through hydrogen bonding and dipolar interactions.[12] Second, given the high efficiency and orthogonality of CuAAC, we expected that sugar residues with free hydroxyl groups could be employed, thus allowing a direct entry to the target unprotected glycoconjugates.

As the first step we decided to introduce the azido group selectively at C40 of rapamycin by exploiting the superior reactivity of the secondary hydroxyl group of the cyclohexane ring[9,13] with respect to the hydroxyl groups at C10 and C28. Thus, the preparation of the known azide **2** from rapamycin **1** via triflate activation of the C40 hydroxyl group followed by treatment with sodium azide, required new and optimized conditions[14] (Scheme 1) with respect to the reported procedure.[13d] It should be pointed out that this method involves an S_N2 process and therefore gives rise to inversion of configuration at C40. This structural modification was already carried out for the preparation of various rapamycin analogs, all featuring new and interesting biological properties.[13b–d]

Thus, we set out to performing the Cu-catalyzed coupling between the azido rapamycin **2** and propargyl *O*- and *S*-glycosides

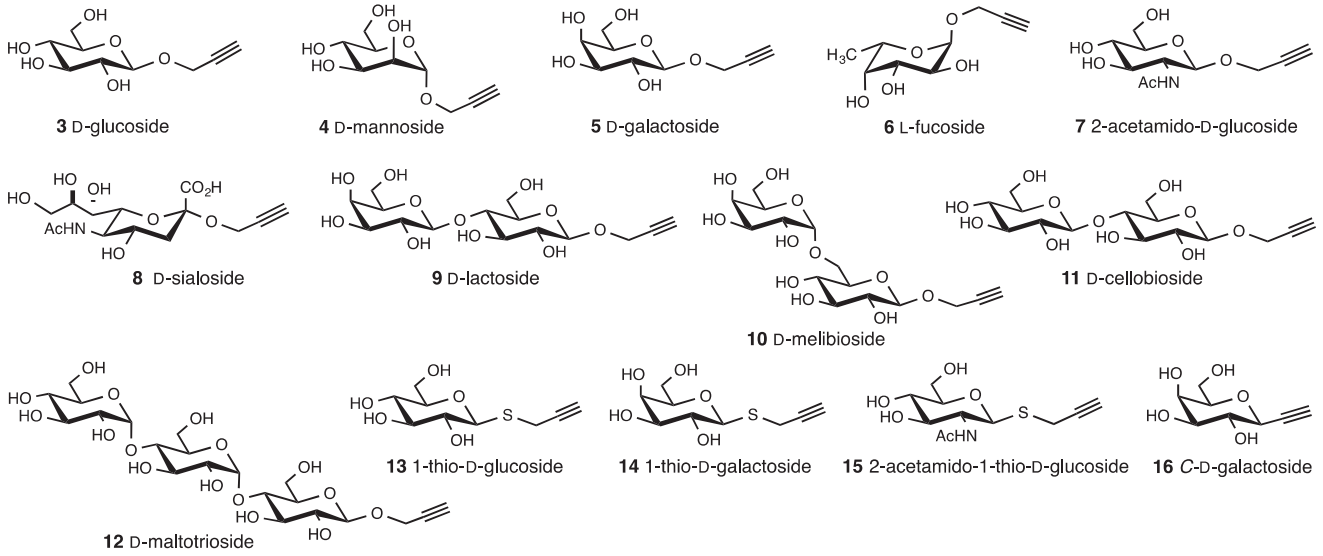
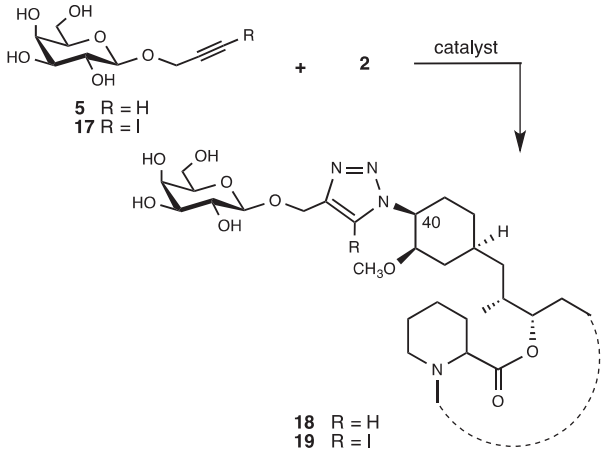


Figure 2. Prepared alkynyl glycosides as reaction partners in the planned cycloadditions with the azido-rapamycin **2**.

Table 1
Screening of catalysts for the cycloaddition of the alkynyl sugar **5** with azido-rapamaycin **2**[a]



Entry	Catalysts and additives	Products (yield)[b] (%)
1	CuI (0.75 equiv)	**18** + **19** (16)
2	CuI (0.75 equiv) DIPEA (1.5 equiv)	**18** + **19** (34)
3	$CuSO_4 \cdot 5H_2O$ (0.6 equiv) Sodium ascorbate (1 equiv)	**18** (64)

[a] Reactions conditions: **5** (3 equiv), DMF–H_2O, rt, 24 h.
[b] Isolated yields after column chromatography.