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Semi-Synthesis of new glycosidic triazole derivatives of dihydrocucurbitacin B

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ABSTRACT

Cucurbitacins are natural triterpenoids to which several biological activities are attributed. These molecules can be isolated as free aglycones or as glycosides, despite cucurbitacin glycosides being difficult to be obtained from natural sources. In this work, we report the synthesis of a new 2-β-*O*-galactoside of dihydrocucurbitacin B and also the synthesis of eight new glycosides containing triazole moiety between the cucurbitane skeleton and the monosaccharidic unit.

Introduction

Cucurbitacins are natural compounds of great interest in medicinal chemistry, mainly due to their previously reported biological activities. Presently, there are over one hundred cucurbitacins described, to which several activities have been attributed, such as laxative, anticancer, antibacterial, antiviral, anti-inflammatory, and antitumoral.[1,2] These highly functionalized triterpenes are found in abundance in plants of the family Cucurbitaceae and may be found as free aglycone or as glycosylated forms, although the glycosides are difficult to obtain from vegetable sources, due to the action of β-glucosidases.[3,4]

Cucurbitacin glycosides presented interesting reports regarding biological activities such as cytotoxic, anti-inflammatory, and antiparasitic.[1,5,6] Some authors suggest selectivity of these compounds against certain cancer cell lines and against *Plasmodium falciparum*.[6,7]

Our research group has been working with isolation and molecular modifications by semi-synthesis in several cucurbitacins, mainly cucurbitacin B (**1**) and dihydrocucurbitacin B (**2**) (Fig. 1).[8,9] Both are isolated in high yields from fruits of *Luffa operculata* and roots of *Wilbrandia ebracteata*, respectively.[9,10] There are few studies regarding semi-synthesis of cucurbitacin derivatives. All works in the literature involve reactions such as oxidation, reduction, acetylation, formation of esters and ethers, etc.[9,11,12] In addition, there is one work which describes the total synthesis of cucurbitacins B and D.[11]

Our previous results encouraged us to synthesize new cucurbitacin glycosides, as there are no reports of synthesis of glycosylated derivatives other than the publication from our research group.[13] These new derivatives may possibly improve biological activity and will enrich SAR studies of this class of compounds.

Results and discussion

Molecular planning

In an earlier work, the isolation and semi-synthesis of novel derivatives of dihydrocucurbitacin B (**1**) and cucurbitacin B (**2**) were reported. The reactions were carried out mainly targeting the C-2, C-16 positions and the side chain. The evaluation of the in vitro cytotoxicity of the new derivatives in non-small-lung cancer cells (A549) showed that the substituents in positions C-2 and C-16 had strong influence on the biological activity. The study also demonstrated that the derivative 16-oxo-dihydrocucurbitacin B (**3**) presented higher cytotoxic activity than its precursor **1**. Modification in C-2 increased or decreased activity, depending on the substituent. For example, addition of the acetoxy group or carbamate substituent reduced the cytotoxic activity, while Br, NH_2, or

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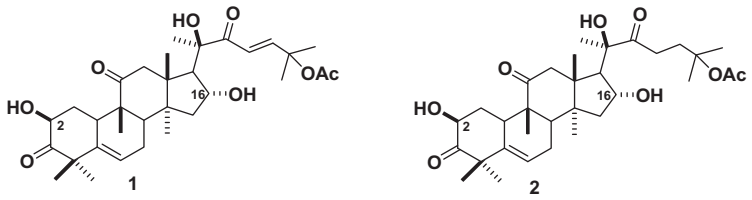

Figure 1. Cucurbitacin B (**1**) and dihydrocucurbitacin B (**2**) isolated from *Luffa operculata* and *Wilbrandia ebracteata*, respectively.

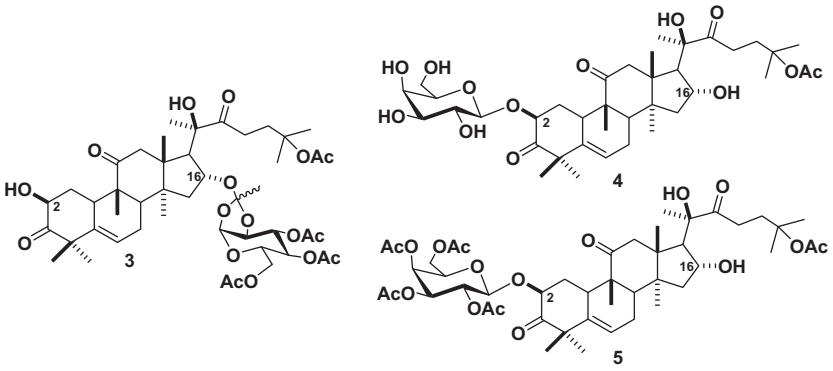

Figure 2. Novel semi-synthetic glycosides of di-hydrocucurbitacin B obtained by Machado and co-workers.[13]

aminothiazole substituent at C-2 showed promising cytotoxic activity. Facing these results, there is still a necessity to further study the role of the substituents at C-2 of dihydrocucurbitacin B and cucurbitacin B, in several biological activities.[9,14]

In previous reports, a series of modified cucurbitacins were synthesized, including three novel glycosides (Fig. 2). The compounds **3**, **4**, and **5** were prepared via classical O-glycosylation reactions, such as Köenigs-Knorr and Schmidt glycosylation.[13] However, these glycosides were obtained in low yields, possibly due to the low nucleophilicity of the hydroxyl group in C-2. This lack of reactivity may be influenced by the ketone present in C-3, forming the α-ketol system.

Continuing the study of Machado and co-workers, the synthesis of *O*-glycosides **6a**–**d** was proposed by direct O-glycosylation at C-2 position of the derivative 16-oxo-dihydrocucurbitacin B, for the study of these modifications facing biological activities (Fig. 3).

Additionally, spacer groups can be added between the monosaccharide moiety and cucurbitane scaffold as a tool of junction between two blocks. Since triazole rings have been included in many compounds which presented several biological activities, such as anticancer, antifungal, and antibacterial, the 1,2,3 triazole groups were used as spacer in this work. Similarly to the monosaccharides, the triazole spacer could play some interesting interaction with biological targets.

A chain extension at C-2 containing terminal bromine enabled the synthesis of various derivatives through classic S_N2 reactions. The replacement of the bromine with azide allows the synthesis of a series of glycosylated dihydrocucurbitacin B derivatives (**7a**–**d**) via cycloaddition reaction with four different monosaccharides containing terminal alkynes. Microwave reactor was used for a Click Chemistry strategy to obtain these proposed derivatives. This methodology offers advantages over conventional methods, as it allowed the obtention of the products in few minutes, in good yields and using small amount of solvent (Fig. 4).

A series of protected triazole derivatives were designed in view of in vitro studies of cytotoxic activity against tumor cell lines, including a QSAR study performed by Bartalis and co-workers, which reported a correlation between increased lipophilicity and increased cytotoxic activity.[11]

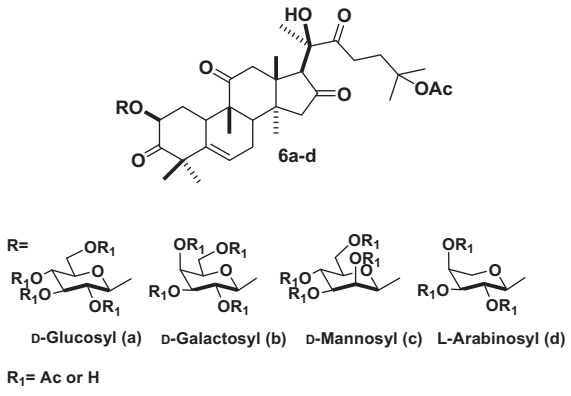

Figure 3. Proposal of new glycosylated dihydrocucurbitacin B derivatives.

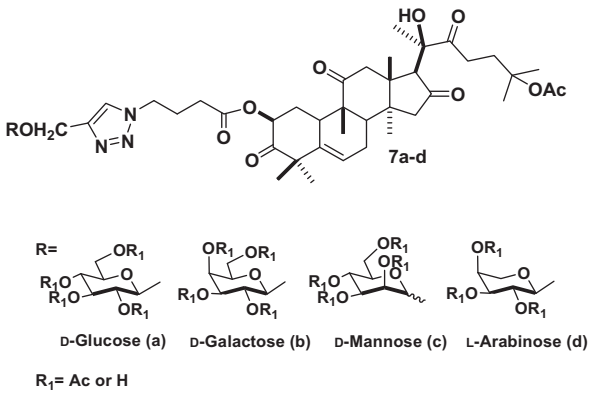

Figure 4. Proposal of new glycosides of dihydrocucurbitacin B using the spacer group between glycosidic unit and the cucurbitacin.