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Minireview

Recent developments in glycosyl urea synthesis

Matthew J. McKay, Hien M. Nguyen *

Department of Chemistry, University of Iowa, Iowa City, IA 52242, United States

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ABSTRACT

The area of sugar urea derivatives has received considerable attention in recent years because of the unique structural properties and activities that these compounds display. The urea-linkage at the anomeric center is a robust alternative to the naturally occurring *O*- and *N*-glycosidic linkages of oligosaccharides and glycoconjugates, and the natural products that have been identified to contain these structures show remarkable biological activity. While methods for installing the β-urea-linkage at the anomeric center have been around for decades, the first synthesis of α-urea glycosides has been much more recent. In either case, the selective synthesis of glycosyl ureas can be quite challenging, and a mixture of α- and β-isomers will often result. This paper will provide a comprehensive review of the synthetic approaches to α- and β-urea glycosides and examine the structure and activity of the natural products and their analogues that have been identified to contain them.

1. Introduction

Replacing the traditional *C–O–C* and *C–N–C* linkages of glycoconjugates and oligosaccharides with a more robust functionality is appealing to the development of carbohydrate-based therapeutics with enhanced bio-availability and remarkable stability against acid and enzymatic hydrolysis;[1] having direct application in the development of anti-diabetic agents[2–5] and aminoglycoside antibiotics.[6,7] In particular, the urea linkage (Fig. 1) at the anomeric center is an interesting candidate for replacing the native *O*- and *N*-linked glycosidic bonds and has the potential to increase resistance to chemical and enzymatic degradation[8] while maintaining the properties of the natural compounds. Urea-linked glycosides also have the potential to serve as small-molecule H-bond donors in asymmetric catalysis[9] and are currently employed in the forest product industry in adhesive mixtures to reduce the level of toxic phenol in furniture and building materials.[10]

Though quite rare in nature, the glycosyl urea linkage has been identified as a component of the glycocinnamoylspermidine (also known as cinodine) antibiotics (Fig. 1), which were isolated and characterized from a soil sample by the Lederle Laboratories in 1977.[11–13] These compounds are of special interest due to their unique structural features and broad-spectrum activity they display against Gram-negative cell lines and Gram-positive aerobes. There are three members in the cinodine family that have been identified (β, γ_1, γ_2) and share a common α-urea linked xylosamine-quinovose core with a cinnamoyl-spermidene tether. Structural variation at the terminal sugar residue is what differentiates the members of this family and accounts for the range in activities they display. The γ-component of cinodine (Fig. 1) is comprised of an inseparable mixture of γ_1 (**2**) and γ_2 (**3**) and is up to 20× more active than β-cinodine (**1**) (in vitro & in vivo studies),[14] which may be explained by the chemically labile carbonyl functionality of the strained oxazolidone (γ_1, **2**) and imidazolidone (γ_2, **3**) *trans*-fused rings which are incorporated at the terminal sugar residue of γ-cinodine.[15] A considerable increase in activity and 12-fold improvement in the safety margin (LD_{50}/ED_{50}) is observed after modifying the γ-structures to the semi-synthetic derivatives, *N*-Isopropyl γ-cinodines (**4**, **5**, Fig. 1).[16,17]

A second class of compounds with the α-glycosyl urea linkage (the coumamidines, **6**, **7**, Fig. 2) was identified and characterized by Abbott Laboratories in 1988.[18,19] The coumamidines are similar in structure to γ-cinodine and differ only by the propanimidine, rather than spermidine, tether they possess. The coumamidines were found to be highly active, as well; distancing themselves from cinodine and aminoglycoside antibiotics by having additional bactericidal activity against anaerobes.[20]

Unlike aminoglycosides, the cinodine and coumamidine antibiotics are not inhibitors of bacterial protein synthesis. Rather, these polycationic structures bind directly to bacterial DNA and even more tightly to gyrase B (organizational enzyme required for bacterial DNA replication); eliciting elongation and filamentation of cells prior to death.[21] This type of targeting is desirable in antimicrobial therapeutics, as the enzyme is known to serve an essential role in cellular function and is presumed to be present in all bacteria.[22]

A third glycosyl urea-containing compound, glycocinnasperimicin D (**8**, Fig. 3), was isolated and characterized by Umezawa at the

* Corresponding author. Tel.: +1 319 384 1887; fax: +1 319 335 1270.
E-mail address: hien-nguyen@uiowa.edu (H.M. Nguyen).

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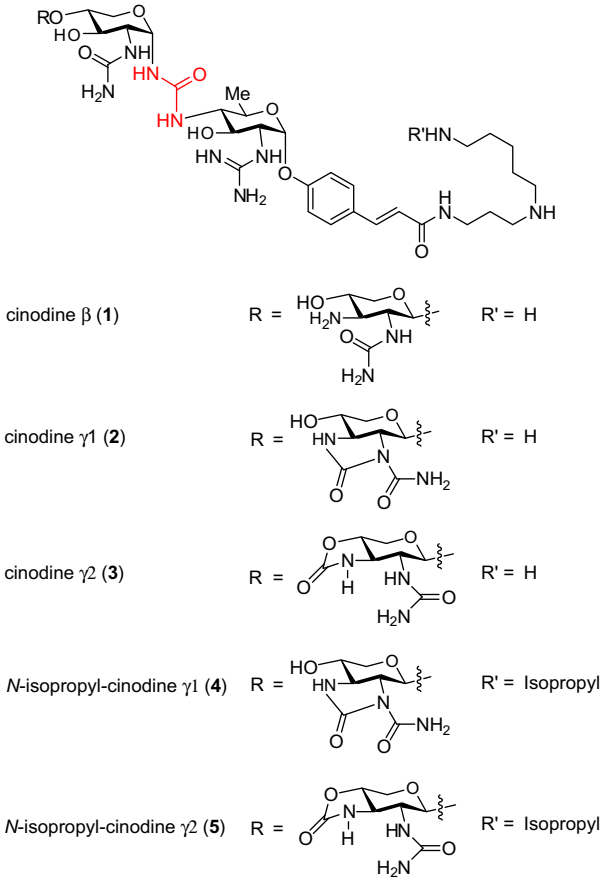

Figure 1. Cinodine antibiotics and semi-synthetic derivatives.

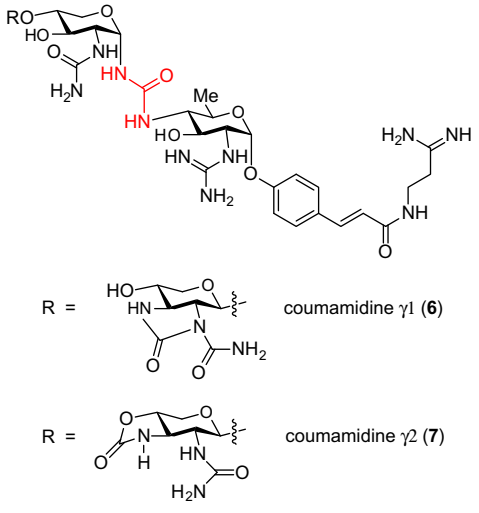

Figure 2. Coumamidine antibacterial agents.

Institute of Microbial Chemistry of Japan in 1985.[23] This compound has the cinnamoyl-spermidine tether in common with cinodine, though it lacks the third sugar residue and has a urea-bridged pseudodisacharide component in the β-orientation, instead of the α-linkage found in the cinodines and coumamidines. A total synthesis of glycocinnasperimicin D (**8**) has been reported by Ichikawa (see Section 2c) and is of added significance because the compound is no longer acquirable from natural sources due to a mutation in the strain of *Nocardia* it was isolated from Ref. [24,25] To the best of our knowledge, a synthesis of the remaining cinodine or coumamidine antibiotics has not been reported due to difficulties associated with the selective construction of the 1,2-*cis*-2-aminosugar urea.

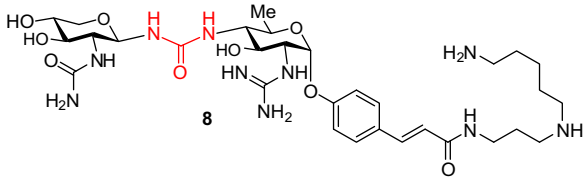

Figure 3. Glycocinnamoylsperimicin D.

The task of synthesizing glycosyl urea is by no means trivial.[26] Approaches are often complicated by numerous steps and there is a propensity for many donor types to undergo anomerization; effectively removing them from consideration in selective urea synthesis. To add to this, the reactivity observed in generating the glycosyl urea-linkage can be highly dependent on the electronic properties and substitution patterns of the coupling partners. This review will be divided into two sections; covering the handful of methods available for the synthesis of β-glycosyl urea; and the few which are able to attain the α-linked urea structure. Each section will be further partitioned on the basis of the type of reactive carbohydrate species used in the formation of urea-glycosides.

2. β-Linked urea glycosides

This detailed overview of the synthetic approaches to urea glycosides will begin by covering reactions available for the synthesis of urea glycosides with the β-orientation at the anomeric center. This was chosen for several reasons: (1) these compounds are generally easier to attain than their α-linked counterparts; (2) there are more synthetic strategies available for constructing the β-compounds; (3) the first reported synthesis of β-urea glycosides predates that of the α- by over a century. For this reason, our review will commence with the oldest of the β-urea syntheses: the acid catalyzed condensation of glucose and urea. This type of reaction requires no protection or deprotection strategies to prepare its coupling partners and, as an interesting side-note, is not only where the synthesis of glycosyl urea would get its start, but is also the focus in some of the most recent advances being made in the field.

2.1. Carbohydrate hemiacetals

It has been more than 100 years since Schoorl first described the crystalline product of the condensation of glucose **9** and urea **10** (Scheme 1).[27,28] At that time, there was report of difficulty in reproducibly detecting the levels of lactose in the urine. This prompted Schoorl to investigate his hypothesis that the sugar was able to evade detection in the urine by somehow existing in combinatorial form with it. The endeavor would lead to the first chemical synthesis of glucosyl ureide **11** (Scheme 1) in 1903,[29] though Schoorl's method would be later characterized as problematic and ill-suited for achieving appreciable quantities from the reaction.[30]

Improvements to Schoorls' method were reported by Hynd in the 1920's after completing his studies as to whether glucose **9** and urea **10** (Scheme 1) would be able to couple under physiological conditions.[31] While that investigation would prove fruitless, Hynd discovered that by heating glucose in an excess of urea to 50 °C in dilute sulfuric acid, as much as 60–70% of the desired