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Original article

Quercitylcinnamates, a new series of antidiabetic bioconjugates possessing α-glucosidase inhibition and antioxidant

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ABSTRACT

Antidiabetic agents possessing dual functions, α-glucosidase inhibition and antioxidant, have been accepted to be more useful than currently used antidiabetic drugs because they not only suppress hyperglycemia but also prevent risk of complications. Herein, we design antidiabetic bioconjugates comprising of (+)-*proto*-quercitol as a glucomimic and cinnamic analogs as antioxidant moieties. Fifteen quercitylcinnamates were synthesized by direct coupling through ester bond in the presence of DCC and DMAP. Particular quercityl esters **6a**, **7a** and **8a** selectively inhibited rat intestinal maltase and sucrose 4–6 times more potently than their parents **6**, **7** and **8**. Of synthesized bioconjugates, **6a** was the most potent inhibitor against maltase and sucrose with IC_{50} values of 5.31 and 43.65 μM, respectively. Of interest, its inhibitory potency toward maltase was 6 times greater than its parent, caffeic acid (**6**), while its radical scavenging (SC_{50} 0.11 mM) was comparable to that of commercial antioxidant BHA. Subsequent investigation on mechanism underlying inhibitory effect of **6a** indicated that it blocked maltase and sucrose functions by mixed inhibition through competitive and noncompetitive manners.

1. Introduction

Type 2 diabetes is characterized by chronic hyperglycemia and the development of microangiopathic complications such as retinopathy, nephropathy and neuropathy. Aggressive control of blood glucose level is preliminary and effective therapy for diabetic patients and reduces risk of complications [1]. Current evidences suggest that excess plasma glucose drives overproduction of superoxide radicals and other reactive oxygen species, which impair the cells via oxidative stress and account for the pathogenesis of all diabetic complications [2–4]. Therefore, antidiabetic drugs possessing antihyperglycemic effect and radical scavenging would be potential for diabetic therapy.

In the course of our research on new α-glucosidase inhibitors, we recently reported the synthesis and inhibitory effects of aminoquercitols [5], conduritol F [6] and inositol analogs from naturally available (+)-*proto*-quercitol (Fig. 1). Although (+)-*proto*-quercitol has five contiguous hydroxy groups on cyclohexane ring, exclusive formation of single bis-acetonide is critical to obtain the desired product without stereogenic congeners, in few steps. In fact, (+)-*proto*-quercitol itself does not show inhibitory activity against α-glucosidase possibly due to its water soluble property that enhances ready absorption by small intestine. However, structural modification of (+)-*proto*-quercitol by installing a series of alkyl and acyl motifs [7] or eliminating hydroxyl group [6] led to new generations of quercitol-based analogs with enhanced activity. With the success of this approach in hand, we expand our application by connecting quercitol core with other bioactive residues.

Inspired by chlorogenic acid (Fig. 2A), a well-recognized natural product having both antioxidant [8] and antidiabetic activities [9], we plan to introduce caffeic acid and other related cinnamic analogs onto quercitol core (Fig. 2B). In the current study, we synthesized fifteen quercitylcinnamates by coupling of (+)-*proto*-quercitol (**10**) and its epimer (**11**) (Scheme 1) with a series of cinnamic analogs (**1**–**8**, Scheme 2). A new series of quercitol-based bioconjugates with improved inhibition were obtained. Structure–activity relationship of the synthesized compounds and mechanism underlying α-glucosidase inhibitory effect of the most potent inhibitor are herein discussed.

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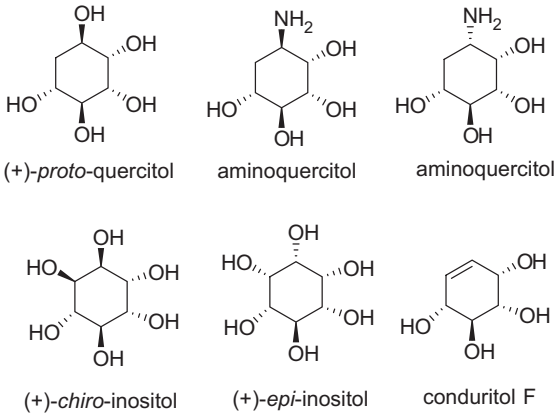

Fig. 1. Structures of (+)-*proto*-quercitol and its synthetic analogs.

2. Results and discussion

2.1. Compound design and synthesis

Crucial to the successful synthesis of all the conjugates described in this work is the selective coupling reaction of cinnamic derivatives with the desired hydroxy group on naturally available (+)-*proto*-quercitol (**9**) (Scheme 1). Bis-acetonides **10** and **11** were prepared from **9**, which was isolated from the stems of *Arfeuillea arborescens* using the procedure described elsewhere [6,7]. Briefly, (+)-*proto*-quercitol was obtained in 0.3% (w/w) yield as white solid after recrystallization by MeOH. Protection of two diols with dimethoxypropane gave the target alcohol **10**. In order to investigate the effect of C-1′ configuration on inhibitory effect, the epimer **11** was also synthesized from **10** through oxidation using acetic anhydride/DMSO followed by $LiAlH_4$ reduction, yielding the desired product in 42% yield.

With the chiral coupling partners **10** and **11** in hands, the quercitylcinnamates **1a**–**8b** were prepared as depicted in Scheme 2. For the esters **1a**–**8a** and their epimers **1b**–**8b**, the synthetic route was straight forward involving the direct coupling reaction between alcohol **10** or **11** with the corresponding cinnamic derivatives **1**–**5** in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). Removal of acetonide group underwent smoothly upon treatment of amberlyst-15 in methanol to give esters **1a**–**5a** in 56–73% yields (Scheme 2).

On the other hand, esterification of caffeic acid (**6**), ferulic acid (**7**) and isoferulic acid (**8**) required additional protection step because free phenolic group(s) of those compounds could interfere with the coupling reaction. The silylation of **6**–**8** with *tert*-butyldimethylsilyl chloride (TBDMSCl) not only prevented phenolic group(s) possibly being esterified but also improved solubility of the acids **6**–**8** in CH_2Cl_2, thus facilitating esterification reaction. The syntheses of quercitylcinnamates **6a**–**8b** were accomplished by ester bond formation of protected cinnamic derivatives with the chiral alcohol **10** or **11** followed by double deprotection of silyl and acetonide groups with TBAF and amberlyst-15, respectively. Esters **6a**–**8b** were then isolated in 42–49% yield as white solid (Scheme 2).

2.2. α-Glucose inhibitory activity and DPPH radical scavenging

All newly synthesized bioconjugates **1a**–**8b** were subjected to evaluate for their α-glucosidase inhibitory effect and antioxidation (Table 1). The commercial antidiabetic drug acarbose was used as the reference and the parent cinnamic analogs (**1**–**8**) were also validated for comparative purpose. For α-glucosidase inhibitory activity, all bioconjugates showed no inhibition against yeast α-glucosidase (type I α-glucosidase) but some of which inhibited maltase and sucrose, type II α-glucosidases from rat intestine. The bioconjugates **6a**–**8b**, whose structures encompassing caffeoyl, feruloyl and isoferulyl moieties, displayed inhibitory effects in range of 5.31–954.08 μM, whereas **1a**–**5a** were not active. Notably, their cinnamoyl cores in **6a**–**8b** different from those of **1a**–**5b** in having at least one phenolic group, suggesting that this moiety possibly involved in exerting the observed inhibition. It was likely that the more phenolic group in cinnamoyl moiety, the more potent inhibition observed. This result was similar to previous report of intestinal α-glucosidase inhibition of hydroxylated cinnamic derivatives **6**, **7** and **8** [10]. This trend was obviously found in **6a**, whose inhibition against maltase was more potent than those of **7a** (10 times) and **8a** (4 times); while **8a** showed only two times more potent than **7a** (Table 2).

Further inspection of two quercityl residues (**10** and **11**), installed in the active bioconjugates, on inhibitory effect revealed significant difference in inhibition. Bioconjugates **6a**, **7a** and **8a**, all of which generated from natural quercitol **10**, showed inhibitory effect 3–94 times more potent than their corresponding C-1′epimers (**6b**, **7b** and **8b**). The difference in inhibitory potency among epimeric analogs was strikingly observed in **6a**, whose inhibition against maltase and sucrose were 93 and 22 times more potent than **6b**. Compared to their corresponding cinnamic precursors (**6**, **7** and **8**), **6a**, **7a** and **8a** showed more improved inhibitory effects (4–6 times), whereas their epimeric analogs (**6b**, **7b** and **8b**) displayed reverse trend (Fig. 3). The observed results suggested that *R* configuration of C-1′ in quercityl moiety was also associated with exerting inhibitory effect, in addition to the presence of more phenolic groups in cinnamoyl residues. The pronounced inhibitions raised by *R* configuration of C-1′ were also supported by a similar trend observed in our previous report of *N*-alkyl aminoquercitols [7]. Of bioconjugates synthesized, **6a** showed most potent inhibition against both maltase and sucrase with IC_{50} values of 5.31 and 43.65 μM, respectively.

As for antioxidation of synthesized bioconjugates, **6a** showed radical scavenging activity toward DPPH with SC_{50} value of

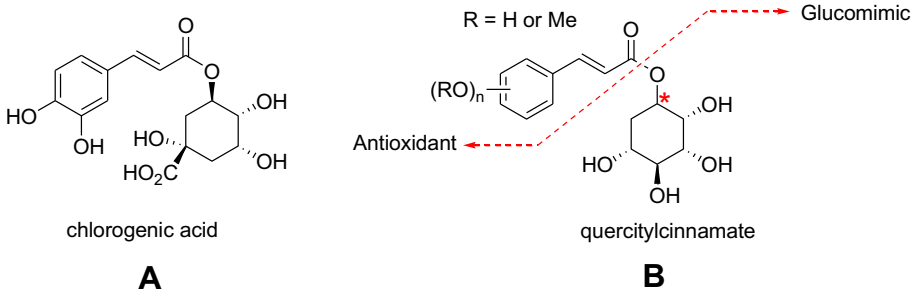

Fig. 2. Structures of chlorogenic acid (**A**) and designed quercitylcinnamates (**B**) encompassing antioxidant and glucomimic residues.