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Toward the development of new α-glucosidase inhibitors from naturally available (+)-proto-quercitol

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α-Glucosidase inhibitors, such as acarbose and voglibose, have been introduced onto the market for treatment of type 2 diabetes. From a structural point of view, most of them are categorized into aminocyclitols or carbasugars. Once aminocyclitols are protonated their shape and charge mimic carbohydrate substrate, thus leading to enzyme inhibition. In addition, conduritols, other kinds of carbasugars having cyclohexene moiety, can also inhibit enzyme by mimicking a half-chair conformation of the substrate. Therefore, a series of aminocyclitols and conduritols have been studied intensively on their potential for the enhancement of α-glucosidase inhibitory activity. Most importantly, many previous data suggested that the potent α-glucosidase inhibitors were developed from their parent by functional modification. With this interesting information, we here in focuses on the development of new α-glucosidase inhibitors starting from naturally available (+)-*proto*-quercitol. We describe the synthesis of *N*-substituted aminocyclitols derived from their parent, aminocyclitols, by the introduction of hydrophobic or hydrophilic moieties at the nitrogen atom. In addition, we prepared a conduritol and inositols by modifying the quercitol core. α-Glucosidase inhibitory activity and kinetic analysis of synthesized compounds were also studied. We have synthesized conduritol and its analogues along with a new series of *N*-substituted aminoquercitols from (+)-*proto*-quercitol. In the first part, we have reported a concise synthesis of (+)-conduritol F, (+)-*chiro*- and (+)-*epi*-inositols using elimination of OTf. Our approach provided the desired products in enantiomerically pure form with excellent overall yield. (+)-Conduritol F showed the highest inhibition against yeast α-glucosidase with an IC_{50} value of 86 μM, which is five times more potent than standard drug, acarbose. In the second part, we have prepared a new series of *N*-substituted aminoquercitols; *N*-alkyl, *N*-aryl series, and drug-like compounds, by introducing hydrophobic and hydrophilic groups onto nitrogen atom. All synthesized compounds showed weak to no inhibition against yeast α-glucosidase. On the other hand, they exhibited strong inhibition against rat intestinal α-glucosidase, particularly maltase. Compounds 1 (*N*-alkyl series), 2 (*N*-aryl series), and 3 (drug-like compound) were the most potent inhibitors of their own series with IC_{50} values of 0.24, 5.6, and 0.53 μM, respectively. The most active compounds (1-3) inhibited the enzyme by competitive manner, the same as antidiabetic drugs.

Biography

Wisuttaya Worawalai has been studying in the Organic Chemistry field from Chulalongkorn University. Her research focused on the synthesis of α-glucosidase inhibitors from naturally available (+)-*proto-quercitol* at Natural Products Research Unit, Department of Chemistry, Faculty of Science, Chulalongkorn University. She has published 5 papers in scientific journals.

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