2-Hydroxyquinoline and Its Structural Analogs Show Antidiabetic Effects against α -Amylase and α -Glucosidase

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Abstract This study investigated the inhibitory activities of 2-hydroxyquinoline and its analogs against α -glucosidase and α -amylase. Based on the IC_{50} values of 2-hydroxyquinoline analogs tested against α -glucosidase and α -amylase, 2-hydroxyquinoline had potent inhibitory activity (64.4 and 130.5 μ g/mL, respectively), while 2-methyl-8-hydroxyquinoline showed weakly inhibitory activity (90.7 and 215.4 μ g/mL, respectively). 2-Methylquinoline demonstrated no activity against α -glucosidase and α -amylase. In conclusion, 2-hydroxyquinoline analogs, with the existence of a methyl group and hydroxyl on quinoline, can be useful as a new diabetes treatment.

Keywords 2-hydroxyquinoline · α -amylase · α -glucosidase · anti-diabetic activity

Diabetes mellitus is a major chronic disease induced by an unsuitable balance of blood glucose, having a significant impact on health (Hu et al., 2008). Diabetes can be divided into type I and type II (Jeong et al., 2012; Lee et al., 2012a). Type I diabetes is an insulin-dependent disease, while type II diabetes (adult type diabetes mellitus) is a non-insulin-dependent disease that accounts for approximately 90% of all diabetes mellitus cases (Toshiro et al., 2001; Lee et al., 2012b). Although type I can effectively be controlled by the regulation of insulin, finding a useful therapy for

the management of type II is difficult (Yang et al., 2011). In this regard, effective methods for hypoglycemic action are needed (Choi et al., 2008). One of the methods of therapy is to decrease the hyperglycemia by delaying the absorption of glucose, accomplished by inhibition of starch breakdown enzymes such as α -amylase and α -glucosidase (Bhandari et al., 2008). Therefore, control of α -amylase and α -glucosidase during hyperglycemia can be a significant approach in the management of high blood glucose connected to type II diabetes (Lee, 2005; Wang et al., 2010; Jeong et al., 2012). Plant-derived materials had been used as alternative materials due to their bioactive substances (Lee and Ahn, 1998; Lee, 2002; Yang et al., 2002). In addition, previous studies have reported that plant-derived materials possess α -amylase and α -glucosidase inhibitory effects (Lee, 2005; Jeong et al., 2012). In this regard, the antidiabetic activities of 2-hydroxyquinoline and its structural analogs against α -amylase and α -glucosidase were evaluated.

Acarbose, 2-hydroxyquinoline, 2-methylquinoline, and 2-methyl-8-hydroxyquinoline were provided from Sigma-Aldrich (USA). All chemicals were of reagent grade. The activities of 2-hydroxyquinoline and its structural analogs were evaluated against α -amylase and α -glucosidase. The α -amylase inhibitory activity was assayed following the procedure described by Wang et al. (2010) and Jeong et al. (2012), with small modifications. The enzyme solution (6.25 U/mL) was laid by dissolving α -amylase (Sigma Co., USA) in 0.5 M Tris-HCl buffer (pH 6.9). The starch azure (8 mg) was suspended in 0.5 M Tris-HCl buffer containing 0.01 M calcium chloride, and was soaked in boiling water for 5 min followed by preincubation at 37°C for 10 min. The enzyme solution (100 μ L) and test sample (100 μ L) in 50% dimethyl sulfoxide were mixed in a 96-well plate. After 10 min, 50% acetic acid (50 μ L) was added to stop the response. The absorbance of the reactants was determined at 595 nm with a microplate reader (Model ASYS UVM 340, Biochrom Ltd., UK). The inhibition percentage (%) was calculated using the following equation: Inhibition (%) = $[1 - (\text{sample absorbance} / \text{control absorbance})] \times 100$. α -Glucosidase inhibitory activity was tested according to the

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procedure described by Shinde et al. (2008) and Jeong et al. (2012), with a slight modification. The formation of *p*-nitrophenol was measured using α -glucosidase after response with *p*-nitrophenyl- α -D-glucopyranoside (NPG). The enzyme solution (0.6 U) was prepared by dissolving α -glucosidase in 0.1 M phosphate buffer (pH 7.0) containing 2 g/L bovine serum albumin and 0.2 g/L sodium azide. The enzyme solution (50 μ L) and sample (10 μ L) dissolved in dimethyl sulfoxide were mixed, and placed in a 96-well plate. After 15 min, 5 mM NPG (50 μ L) in the identical buffer was added, and the mixture was incubated for 10 min at 37°C. After 10 min, 0.1 M Sodium carbonate was added to stop the reaction. The absorbance of the reactants was measured at 405 nm using a microplate reader (Model ASYS UVM 340, Biochrom Ltd.). Inhibition percentage (%) was calculated using the equation above for amylase activity. Acarbose was used as a positive control in all experiments. All tests were performed in triplicate. The IC₅₀ values were calculated using the logarithmic regression analysis.

The inhibitory effects of 2-hydroxyquinoline and its structural analogs (2-methylquinoline, 2-methyl-8-hydroxyquinoline) against α -amylase and α -glucosidase are presented in Table 1. Including the information for the acarbose positive control, the IC₅₀ value of 2-hydroxyquinoline demonstrated the strongest inhibitory activity against α -glucosidase (64.4 $\pm$ 1.7 μ g/mL), followed by acarbose (66.5 $\pm$ 1.5 μ g/mL), and 2-methyl-8-hydroxyquinoline (90.7 $\pm$ 2.5 μ g/mL). In contrast, 2-methylquinoline was found to have no activity against α -glucosidase. Based on the IC₅₀ values of acarbose, 2-hydroxyquinoline and its structural against α -amylase, 2-hydroxyquinoline (130.5 $\pm$ 2.2 μ g/mL) had potent α -amylase inhibitory activity, followed by acarbose (180.6 $\pm$ 1.3 μ g/mL), and 2-methyl-8-hydroxyquinoline (215.4 $\pm$ 1.4 μ g/mL) (Table 1). Like for α -glucosidase, 2-methylquinoline also showed no activity against α -amylase.

To confirm a structure-activity relationship and to determine the role of functional groups for the antidiabetic effects of 2-hydroxyquinoline analogs, its structural analogs were evaluated based on their antidiabetic activities. The importance of the functional groups was estimated by comparing IC₅₀ values. 2-Hydroxyquinoline, which was the hydroxyl-containing quinoline

Fig. 1 Structures of 2-hydroxyquinoline derivatives; (A) 2-hydroxyquinoline; (B) 2-methylquinoline; (C) 2-methyl-8-hydroxyquinoline.

(Fig. 1), showed strong inhibitory effects for both α -amylase and α -glucosidase. According to previous studies, the combination with hydroxyl can be an essential content for antidiabetic activity (Miura et al., 1996). On the other hand, 2-methyl-8-hydroxyquinoline, which adds a methyl group to the hydroxyquinoline (Fig. 1), exhibited hypoglycemic effects comparable to acarbose. 2-Methylquinoline, which introduced the methyl group in quinoline (Fig. 1), had no antidiabetic activity. Similarly, it has been reported that compounds combined with methyl groups can have reduced hypoglycemic activity (Matsuda et al., 1998). Based upon these results, the inhibitory effects against α -amylase and α -glucosidase can be varied by adding a functional group into hydroxyquinoline.

On the basis of the Material Safety Data sheet provided by Sigma-Aldrich (2013), the oral lethal dose of 2-hydroxyquinoline was not reported for mammals. Furthermore, 2-hydroxyquinoline has been not reported the side effects on human's body. Taken together with this result, 2-hydroxyquinoline derivatives could be used as a new diabetes treatment.

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Table 1 α -Glucosidase and α -amylase inhibitory activities of 2-hydroxyquinoline derivatives

Samples	Anti-diabetic activity	
	α -glucosidase inhibition IC ₅₀ (μ g/mL) ^a	α -amylase inhibition IC ₅₀ (μ g/mL)
2-Hydroxyquinoline	64.4 $\pm$ 1.7	130.5 $\pm$ 2.2
2-Methylquinoline	NI ^c	NI
2-Methyl-8-hydroxyquinoline	90.7 $\pm$ 2.5	215.4 $\pm$ 1.4
Acarbose ^b	66.5 $\pm$ 1.5	180.6 $\pm$ 1.3

^aIC₅₀ values calculated from regression lines, using five different concentrations tested in triplicate.

^bAcarbose was used as a positive control.

^cNI: No inhibition at a concentration of 1,000 μ g/mL.

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