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Sulfonamide chalcone as a new class of α-glucosidase inhibitors

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Abstract—Chalcones **1**–**20**, a new class of glycosidase inhibitors, were synthesized, and their glycosidase inhibitory activities were investigated. Non-aminochalcones **1**–**12** had no inhibitory activity, however, aminochalcones **13**–**20** had strong glycosidase (α-glucosidase, α-amylase, and β-amylase) inhibitory activities. In particular, sulfonamide chalcones **17**–**20** had more potent α-glucosidase inhibitory activity than aminated chalcone **13**–**16**. 4′-(*p*-Toluenesulfonamide)-3,4-dihydroxy chalcone **20** (IC_{50} = 0.4 μM) was the best inhibitor against α-glucosidase, and these sulfonamide chalcones showed non-competitive inhibition.

Screening of glycosidase inhibitors is becoming increasingly prevalent because glycosidases are responsible for the processing and synthesis of complex carbohydrates, which are essential in numerous biological recognition processes.[1] Inhibitors of these enzymes are important molecular tools for glycobiology and can be used to modulate cellular functions.[2] Furthermore, in cases where the control of oligosaccharide metabolism can be linked to cellular dysfunction, they are potential drugs.[3] α-Glucosidases (EC 3.2.1.20) are exo-acting carbohydrases, catalyzing the release of α-D-glucopyranose from the non-reducing ends of various substrates,[4] and also these enzymes are key enzymes in the processing of glycoproteins and glycolipids.[1] Inhibitors can retard the uptake of dietary carbohydrates and suppress postprandial hyperglycemia, and may be useful to treat diabetic or obese patients.[5] This enzyme is a target for inhibition by antiviral agents that interfere with the formation of essential glycoproteins required in viral assembly, secretion, and infectivity.[6] Consequently, many efforts have been made to develop α-glucosidase inhibitors for the treatment of diseases such as diabetes,[5] viral diseases,[6] and cancer.[7] However, most of developed glycosidase inhibitors are sugar mimics (aza sugars,[8] isoxazoles,[9] and aminosugars[10]) which require tedious multi-steps from carbohydrate and non-carbohydrate (Fig. 1).

Recently, we have found that aminated chalcones have the potential to act as a new class of highly specific α-glucosidase inhibitors, which can be obtained with the simple steps economically.

Chalcones, considered as the precursor of flavonoids and isoflavonoids, are abundant in edible plants,[11] and have also been shown to display a diverse array of pharmacological activities, among which anti-protozoal,[12] anti-inflammatory,[13] immuno-modulatory,[14] nitric oxide inhibitory,[15] anticancer,[16] and anti-HIV activities,[17] have been cited in the literature. But, to the best of our knowledge there is, to date, no report that chalcone derivatives have any inhibitory activity against glycosidase. Chalcone is a biosynthetic product of shikimate pathway and can be easily obtained through

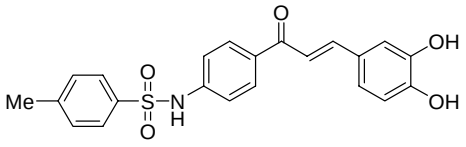

Figure 1.

Keywords: Chalcone; Sulfonamide chalcone; α-Glucosidase inhibitor; Amylase.
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the Claisen–Schmidt condensation of hydroxy acetophenone or carboxy acetophenone using either basic[18] or acidic catalysis.[19] The chalcone products (**1**–**8**) described were prepared from acetophenone and benzaldehyde using catalytic amount of H_2SO_4 in MeOH and some phenolic compounds (**9**–**12**) which were purchased from Sigma Co. (Fig. 2).

The synthesized and purchased chalcones were tested for their enzymatic inhibitory activities against three glycosidases (α-glucosidase from baker's yeast, α-amylase from *Bacillus licheniformis*, and β-amylase from barley). The glycosidases were assayed according to standard procedures by following the hydrolysis of nitrophenyl glycosides spectrophotometrically or by evaluating the reducing sugar formed in amylase assays.[8]

Chalcone derivatives **1**–**12** had no inhibitory activities at 200 μM concentration, but aminated chalcones **15** and **16** had strong inhibitory activities at 200 μM concentration for three glycosidases. Anti-diabetic sulfonylureas[20] have encouraged us to design and synthesize sulfonamide chalcones to develop a more potent new class of glycosidase inhibitors. All sulfonamide chalcone products **17**–**20** were obtained through sulfonylation of aminoacetophenone with *p*-toluenesulfonylchloride and the condensation of sulfonylated acetophenone and benzaldehyde using a catalytic amount of H_2SO_4 in MeOH (Table 1).[21] The synthetic sulfonamide chalcones **17**–**20** were tested for α-glucosidase inhibitory activities, and the results of their inhibitory activities are summarized in Table 2. The α-glucosidase inhibitory activities of sulfonamide chalcones **17** (IC_{50} = 12.4 μM), **18** (IC_{50} = 15.6 μM), **19** (IC_{50} = 1.0 μM), and **20** (IC_{50} = 0.4 μM) have improved progressively compared with aminated chalcones **15** (IC_{50} = 41.0 μM), **16** (IC_{50} = 62.1 μM), **13** (IC_{50} = >200 μM), and **14** (IC_{50} = >200 μM). Especially, sulfonamide chalcone **20** showed 150-fold stronger inhibitory activity than acarbose (IC_{50} = 60.8 μM) as well-known α-glucosidase inhibitor.

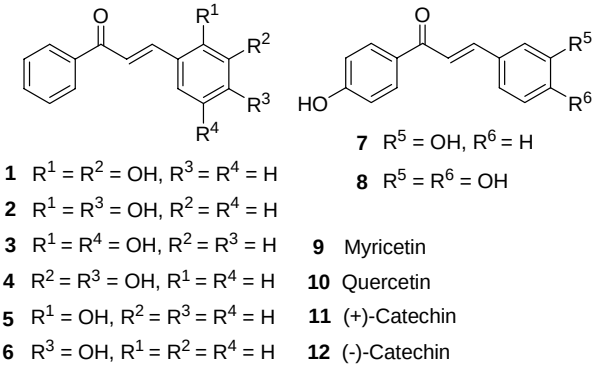


Figure 2. Target chalcones for glycosidase inhibition.

The type of inhibition was analyzed by Lineweaver–Burk plots (Fig. 3), which showed that compound **20** behaves as a non-competitive inhibitor because V_{max}

Table 2. Inhibitory activities of chalcones

Compound	IC_{50} (μM)	
	α-Amylase	β-Amylase
13	NI[a]	206.5
14	NI	NI
15	268.9	NI
16	NI	126.8
17	37.3	201.4
18	16.8	24.8
19	87.8	247.3
20	193.7	65.0

[a] NI means no inhibition (less than 20% inhibition at 200 μM).

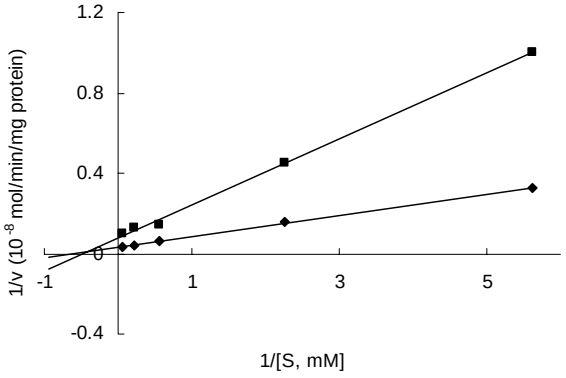
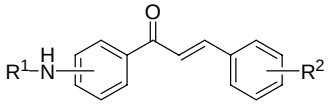


Figure 3. Lineweaver–Burk plot analysis of the inhibition kinetics of α-glucosidase inhibitory effects by compound **20** [■, 0.5 μM inhibitor; ♦ control].

Table 1. Synthetic eight aminated chalcones



Compound	R^1	R^2	IC_{50}, (K_i, μM) α-glucosidase
13	3-H	4-Hydroxy	>200
14	3-H	3,4-Dihydroxy	>200
15	4-H	4-Hydroxy	41.0
16	4-H	3,4-Dihydroxy	62.1
17	3-*p*-Tosyl	4-Hydroxy	12.4 (7.38), non-competitive
18	3-*p*-Tosyl	3,4-Dihydroxy	15.6 (9.25), non-competitive
19	4-*p*-Tosyl	4-Hydroxy	0.98 (0.58), non-competitive
20	4-*p*-Tosyl	3,4-Dihydroxy	0.40 (0.24), non-competitive

values were affected by increasing concentrations of **20**, while the K_m were not. All compounds were screened for two amylase inhibitory activities at 200 μM concentration.

Compounds **1**–**12** did not have inhibitory activity against α-amylase and β-amylase; however, sulfonamide chalcones **17**–**20** were strong inhibitors against α-amylase and β-amylase, and aminated chalcones (**13**, **16**) had mild inhibitory activity against β-amylase (Table 2).

In conclusion, the results show that sulfonamide chalcones represent a new class of strong glycosidase inhibitors.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2005.08.087.

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21. (a) Selected spectroscopic data **17**: mp 183–184 °C; ^{1}H NMR (300 MHz, δ) 2.35 (3H, s), 6.86 (2H, dd, J = 6.8, 1.9 Hz), 7.29 (2H, d, J = 8.3 Hz), 7.37 (3H, m), 7.58 (2H, m), and 7.69 (5H, m); (b) **18**: mp 189–190 °C; ^{1}H NMR (300 MHz, δ) 2.35 (3H, s), 6.85 (1H, d, J = 8.2 Hz), 7.07 (1H, dd, J = 8.3, 2.0 Hz), 7.18 (1H, d, J = 2.0 Hz), 7.27–7.39 (5H, m), 7.62 (1H, d, J = 15.6 Hz), and 7.68 (4H, m); (c) **19**: mp 105–107 °C; ^{1}H NMR (300 MHz, δ) 2.25 (3H, s), 6.82 (2H, d, J = 8.6 Hz), 7.23 (4H, m), 7.42 (1H, d, J = 15.5 Hz), 7.51 (2H, d, J = 8.6 Hz), 7.66 (1H, d, J = 15.5 Hz), 7.73 (2H, d, J = 8.3 Hz), and 7.90 (2H, dd, J = 8.7, 2.0 Hz); (d) **20**: mp 179–180 °C; ^{1}H NMR (300 MHz, δ) 2.29 (3H, s), 6.78 (1H, d, J = 8.2 Hz), 6.94 (1H, dd, J = 8.2, 2.0 Hz), 7.10 (1H, d, J = 2.0 Hz), 7.19 (5H, m), 7.50 (1H, d, J = 15.2 Hz), 7.66 (2H, d, J = 8.2 Hz), and 7.76 (2H, d, J = 8.6 Hz).